The influence of body mass index on airway resistance in children with Asthma: A longitudinal study based on impulse oscillometry

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Abstract

Backgrounds: Obesity is a significant risk factor for asthma, with higher body mass index (BMI) linked to impaired respiratory function. However, the confounding factor of comorbidities, such as Sickle Cell Disease (SCD), is often overlooked. **Methods:** Using Impulse Oscillometry data from 74 African American children (39 with SCD), we applied Generalized Linear Mixed Models to explore the relationship of BMI and airway resistance and reactance of asthma patients, adjusting for age, gender, pharmacotherapy, and SCD, while incorporating BMI-gender interactions. **Results:** Higher BMI was associated with reduced total airway resistance ($p = 0.0096$), central airway resistance ($p = 0.0378$), and resonant frequency ($p < 0.0001$). A significant BMI-gender interaction for resonant frequency ($p = 0.0321$) indicated gender-specific effects. **Conclusions:** BMI negatively impacts airway resistance and reactance in Asthma, with gender-specific differences. Tailored interventions are crucial for improving respiratory health.

Keywords: Asthma, BMI, Impulse oscillometry, Pulmonary function test

1. Introduction

Asthma is a common chronic pulmonary disease characterized by symptoms such as coughing, wheezing, and difficulty breathing, affecting individuals of all ages [1]. Research has shown that obesity is a significant risk factor for asthma, with a higher Body Mass Index (BMI) often preceding the appearance of asthma symptoms and adversely affecting respiratory mechanics by decreasing lung compliance. Moreover, the link between obesity and asthma varies by gender, with existing studies showing inconsistent results and many overlooking the confounding influence of potential comorbidities [2]. In this study, we innovatively include the diagnosis of Sickle Cell Disease (SCD), a common complication of asthma, as a confounder. The presence of SCD can significantly alter airway resistance and reactance.

We used Impulse Oscillometry (IOS), a non-invasive, effort-independent pulmonary function testing method, to evaluate these effects. IOS effectively measures airway resistance and reactance, critical indicators for assessing the severity of obstructive airway diseases in children with asthma. IOS measures both total and central airway resistance (at 5 Hz and 20 Hz, respectively) and reactance, providing precise data on the impact of BMI on respiratory mechanics [3].

To analyze the complex interactions among these variables, we employed Generalized Linear Mixed Models (GLMM), adjusting for confounders including SCD diagnosis, age, gender, and pharmacotherapy history, also including a BMI by gender interaction. Medications such as inhaled corticosteroids (ICS) and long-acting bronchodilators

(LABA), which are fundamental in managing asthma, significantly influence airway resistance and reactance. Additionally, Hydroxyurea, used to maintain pulmonary function in SCD patients, must also be considered in our models [3]. This study aims to improve clinical management for asthma in children, ultimately seeking to improve the quality of life for this vulnerable population.

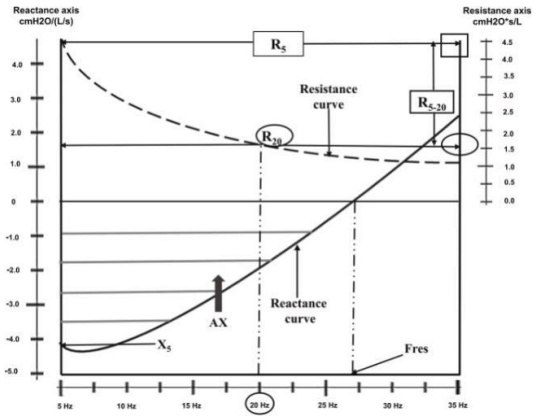


Figure 1. IOS graph. The Y-axis of an IOS graph represents the estimated airway resistance and reactance, while the X-axis represents the soundwave frequency. The airway resistance at 5 Hz (R_5) and 20 Hz (R_{20}) estimates total and central airway resistance, respectively. The difference between R_5 and R_{20} is called R_{5-20} or peripheral resistance. X_5 represents the reactance estimate at 5 Hz frequency, which is −4.0 cmH2O/(L/s). The frequency at which the reactance slope crosses the horizontal line (27 Hz in the figure), is known as the resonant frequency (Fres).

2. Methods

2.1. Study Subjects

This study builds on prior research that evaluated the impact of BMI on IOS

parameters in children with Sickle Cell Disease (SCD), accounting for asthma as a potential confounder [3]. That foundational study involved a retrospective chart review from 2015 to 2020 at a tertiary children's hospital, focusing on 140 children diagnosed with SCD. From this cohort, 55 children regularly attended a comprehensive SCD clinic and underwent routine IOS testing. An additional reference group included 35 African American children with asthma but without SCD. Notably, within the SCD cohort, 39 children had an asthma diagnosis, highlighting the significant overlap between SCD and asthma symptoms.

For each clinic visit, data collected included the patient's age in months, BMI (kg/m^2), and medication status—specifically whether the children were receiving ICS and LABA, or Hydroxyurea therapy for SCD. IOS measurements focused on total airway resistance (R_5), central airway resistance (R_{20}), peripheral resistance (R_{5-R20}), and reactance metrics such as X_5 and resonant frequency (Fres), with estimates expressed as percent predicted using the Lechtenbörger equation.

Our study advanced this previous work by adjusting for the confounding effects of SCD on the relationship between BMI and IOS in children diagnosed with asthma. Our research group consists of 74 patients, combining 39 SCD patients with asthma and the original 35 African American asthmatic children without SCD. This expanded analysis aims to better understand how BMI influences asthma-related pulmonary function outcomes, as measured through IOS.

2.2. Model Overview

To investigate the influence of BMI on IOS outcomes in children diagnosed with Asthma, we employed a GLMM. Given the longitudinal nature of our data, coupled with its relatively small sample size, GLMM was chosen over Generalized Estimating Equations (GEE) due to several advantages:

1) GLMM offers the advantage of adjusting for missing data without requiring further imputation and excluding the observation listwise if any data point is missing [3].
2) GLMM uses maximum likelihood estimation, which tends to yield more reliable results in smaller datasets. This is particularly beneficial for our study, which includes only 74 patients, potentially enhancing the robustness of the findings.
3) Our data vary in the number of observations per patient, with counts ranging from 1 to 6 across the 74 patients. GLMM can accommodate the imbalance.

We evaluated the impact of BMI on various IOS parameters including R_5, R_{20}, $R_{5\text{-}20}$, X_5, and Fres. Our model incorporated fixed effects for BMI, SCD diagnosis, gender, age, and pharmacotherapies (Hydroxyurea, ICS, and LABA), along with an interaction term between gender and BMI. For continuous IOS measures, we fit the model with Gaussian family and an identity link function. We included random intercepts in our model, and the inclusion of random slopes was determined by the Akaike Information Criterion (AIC) to ensure optimal model fit. The general formula

for the model is:

$$Y_{ij} = \beta_0 + \beta_1 \text{BMI}_{ij} + \beta_2 \text{SCD}_i + \beta_3 \text{Gender}_i + \beta_4 \text{Age}_{ij} + \beta_5 \text{Hydroxyurea}_{ij} + \beta_6 \text{ICS}_{ij} + \beta_7 \text{LABA}_{ij} + \beta_8 (\text{Gender}_i \times \text{BMI}_{ij}) + b_{0i} + b_{1i} \text{BMI}_{ij} + \epsilon_{ij}$$

Y_{ij}: IOS parameter (R_5, R_{20}, $R_{5\text{-}20}$, X_5 and Fres) for the ith subject at the jth observation.

$\beta_0 \; to \; \beta_8$: Fixed effect coefficients for the intercept and covariates.

BMI_{ij}: BMI (kg/m^2) of the ith subject at the jth observation.

Gender_i: Gender of the ith subject, which remains constant across observations.

SCD_i: SCD diagnostics of the ith subject.

Age_{ij}: Age in months of the ith subject at the jth observation.

ICS_{ij}: Consumption status of ICS of the ith subject at the jth observation.

LABA_{ij}: Consumption status of LABA of the ith subject at the jth observation.

Hydroxyurea_{ij}: Consumption status of Hydroxyurea of the ith subject at the jth observation.

b_{0i}: Random intercept for the ith subject.

b_{1i}: Random slope for BMI of ith subject, set to zero for random intercept model.

ϵ_{ij}: Random error term of the ith subject at the jth observation.

3. Results

3.1. Summary Statistics

Our dataset comprises observations from 74 patients, with each patient observed

between one and six times. Specifically, 27 patients had a single observation, 18 were observed twice, 11 had three, 15 four, two had five, and one patient had six observations, demonstrating variability in follow-up frequencies.

The cohort consists of 32 males and 42 females, with static gender attributes over time. SCD diagnosis is present in 39 patients, with the remaining 35 undiagnosed. Hydroxyurea was used by 28 patients, whereas 46 did not use it. Treatment involving ICS and LABA varied for 25 patients during the study. Baseline summary statistics are in Table 1.

In an observational analysis of height versus age, most patients showed a typical upward trend. Exceptions include patient ID 89, who showed a decrease in height from 135 cm at 90 months to 133 cm at 93 months, and patient ID 82, who decreased from 185 cm at 213 months to 182 cm at 221 months. These deviations are likely due to measurement errors.

Within our dataset, Fres was the only variable with missing data, showing 10 unrecorded values out of 172, which were missing at random[3]. For the IOS parameters, our analysis identified outliers, based on z-scores exceeding ± 3. We excluded outliers from the final interpretation to ensure the robustness of our results.

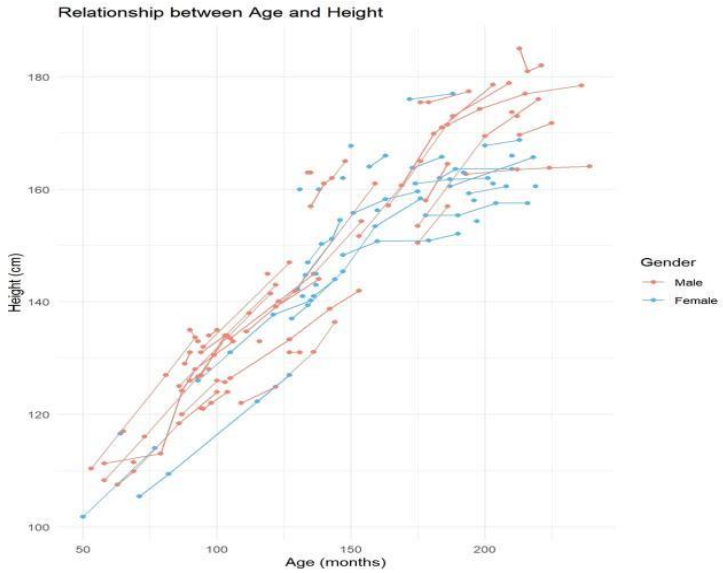


Figure 2. Height (cm) over age for each patient

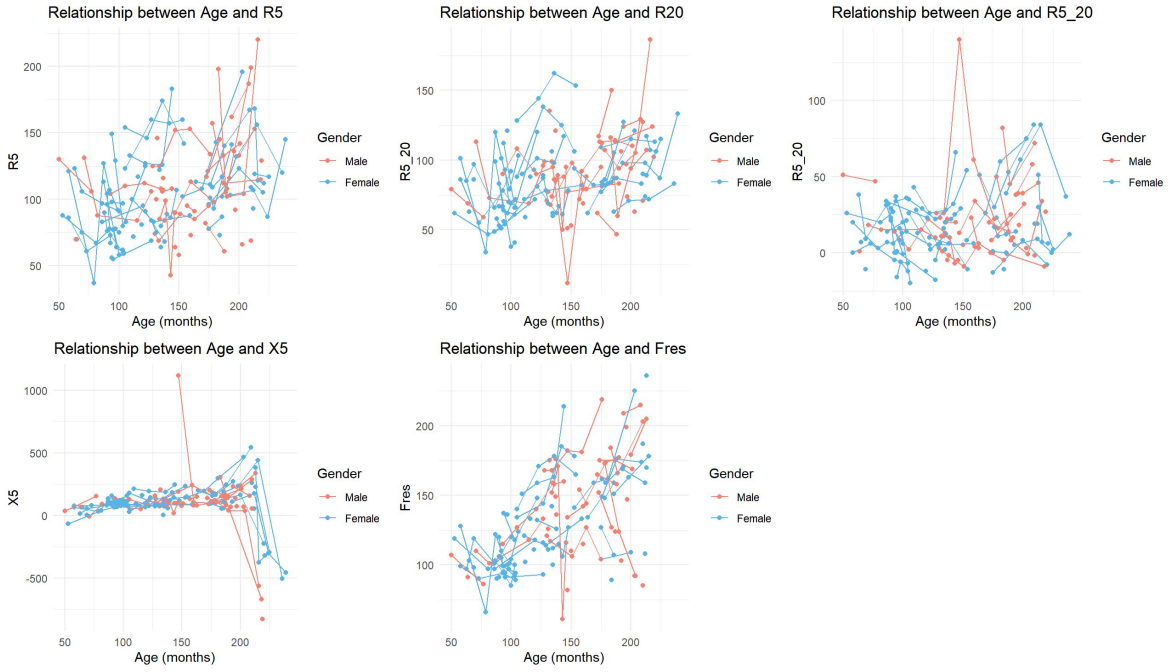


Figure 3. IOS parameters over age for each patient

Table1. Summary statistics for patients at baseline.

Covariates	**Summary Statistics** *
Age (month)	136.0 (79.5)
BMI (kg/m^2)	18.4 (6.4)
SCD (Yes/No)	39 : 35
Gender (Male)	32 : 42
ICS (Yes/No)	46 : 28
LABA (Yes/No)	55 : 19
Hydroxyurea (Yes/No)	28 : 46
Height (cm)	147.7 (31.5)
Weight (kg)	42.9 (28.2)
R5 score	100.5 (42.0)
R20 score	84.5 (33.5)
R5-20 score	13.00 (22.75)
X5 score	88.5 (66.5)
Fres score	124.0 (49.0)

* Median (IQR) for continuous variables and counts for binary variables.

3.2. The influence of BMI on airway resistance and reactance (GLMM)

In our analysis, we utilized a random intercept model to assess the data as it showed a lower AIC compared to random intercept/slope model.

Significant effects were observed after excluding outliers, particularly for the R5, R20,

and Fres parameters. An increase in BMI was associated with decreases in R_5 (β = -1.4546, p = 0.0096), R_{20} (β= -0.9233, p = 0.0378), and Fres (β= -2.7355, $p < 0.0001$). Notably, R_5 represents total airway resistance, R_{20} central airway resistance, and Fres the resonant frequency, collectively demonstrating an inverse relationship between BMI and respiratory function. Furthermore, the interaction between BMI and gender (gender=1 for male) was significant for Fres (coefficient = 1.6704, p = 0.0321), indicating that the impact of BMI on respiratory function differs by gender. These findings underscore the importance of considering gender differences when evaluating the influence of BMI on airway resistance and reactance. The results are shown in Table 2.

Table 2. The influence of BMI on airway resistance and reactance.

IOS	N [a]	Covariate	Estimate	95% Confidence Interval	*P*-value
R_5	171	BMI	-1.4546	(-2.4870, -0.3949)	0.0096 *
		BMI : GENDER	0.9348	(-0.6394, 2.4900)	0.2618
R_{20}	171	BMI	-0.9233	(-1.7447, -0.0841)	0.0378 *
		BMI : GENDER	0.4363	(-0.8057, 1.6705)	0.5081
R_{5-20}	171	BMI	-0.36922	(-1.0892, 0.3580)	0.3360
		BMI : GENDER	0.31920	(-0.7894, 1.4211	0.5860
X_5	166	BMI	-2.9426	(-6.6896, 0.8054)	0.1405
		BMI : GENDER	-0.5011	(-5.9902, 4.9254)	0.8629
Fres	162	BMI	-2.7355	(-3.6889, -1.7655)	< 0.0001 *
		BMI : GENDER	1.6704	(0.2151, 3.1080)	0.0321 *

[a] Number of observations after excluding outliers for 74 patients.

[*] Statistically significant, *P*-value < 0.05.

4. Discussion

Our study demonstrates a significant inverse relationship between BMI and respiratory function in asthma, as evidenced by decreases in total airway resistance, central airway resistance, and resonant frequency with increasing BMI. These findings indicate that higher BMI and obesity are associated with impaired respiratory mechanics in asthma patients. Furthermore, the significant interaction between BMI and gender for Fres suggests that BMI impacts respiratory function differently in males and females, highlighting the need to account for gender differences when evaluating airway resistance and reactance.

This inverse relationship is consistent with prior epidemiological studies that link increased BMI to poorer asthma control and respiratory impairment [4, 5]. The underlying mechanisms likely involve genetic and environmental factors, as both asthma and obesity are multifactorial diseases. BMI-related genes have been associated with asthma, and gene-environment interactions and Mendelian randomization studies further support a causal role for BMI-associated genetic variants in asthma risk. Additionally, in children and adolescents, the relationship between BMI and asthma is often bidirectional, with asthma history and medication use increasing the likelihood of obesity [2].

Gender-specific differences in BMI's impact on respiratory function are consistent with previous findings and may be explained by biological factors. In women, obesity-related hormonal changes, particularly involving estrogen and progesterone, can influence airway reactivity and inflammation. In men, underweight and malnutrition during critical growth periods may impair lung development, contributing to gender disparities in respiratory outcomes [5].

Despite these findings, our study has limitations. First, the sample consisted exclusively of African American children, which may limit the generalizability of findings to other populations. Second, the small sample size reduces statistical power and may limit the detection of subtle effects. Lastly, while our results show a linear relationship between BMI and respiratory function, some studies suggest the relationship may be J-shaped or nonlinear, which our analysis may not fully capture.

In conclusion, our findings reveal a significant inverse relationship between BMI and respiratory function, with notable gender-specific differences. These results highlight the need for tailored interventions that address BMI and gender to improve respiratory health in asthma patients. Future research should explore potential nonlinear effects of BMI on asthma, including more diverse populations, and investigate alternative obesity measures, such as body composition, to provide a more comprehensive understanding of these complex relationships.

5. Data Availability

Mondal, Pritish (2023), “Impact of BMI on IOS measures”, Mendeley Data, V1.

6. References

[1] GBD 2019 Diseases and Injuries Collaborators (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet,* 396(10262):1562.

[2] Peters, U., Dixon, A.E., Forno, E. (2018). Obesity and asthma. *The Journal of Allergy and Clinical Immunology,* 141(4), 1169–1179.

[3] Mondal, P., Padilla Lopez, S., Khokhar, A., et al. (2024). The influence of body mass index on airway resistance in children with sickle cell disease: A longitudinal study based on impulse oscillometry. *Respiratory Medicine,* 224, 107564.

[4] Lavoie, K.L., Bacon, S.L., Labrecque, M., et al. (2006). Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respiratory Medicine,* 100(4), 648–657.

[5] Kang, M., Sohn, S.J., Shin, M.H. (2020). Association between Body Mass Index and Prevalence of Asthma in Korean Adults. *Chonnam Medical Journal,* 56(1), 62–67.

7. Appendix

```r
library(tidyverse)
library(summarytools)
library(lme4)
library(lmerTest)
library(gridExtra)
knitr::opts_chunk$set(tidy.opts=list(width.cutoff=40), tidy=TRUE)
knitr::opts_chunk$set(echo = TRUE, results = 'hide')
```

```r
data <- read.csv("D:/P8157_FINAL/BMI_IOS_SCD_Asthma.csv")
# check variables
data_grouped <- data |>
    filter(Group == "C-SCD") |>
    arrange(Subject.ID, Observation_number)

subjects_always_yes <- data_grouped |>
    group_by(Subject.ID) |>
    summarise(All_Yes = all(Asthma == "Yes",
        na.rm = TRUE)) |>
    filter(All_Yes == TRUE)

subjects_always_no <- data_grouped |>
    group_by(Subject.ID) |>
    summarise(All_Yes = all(Asthma == "No",
        na.rm = TRUE)) |>
    filter(All_Yes == TRUE)
nrow(subjects_always_yes)
nrow(subjects_always_no)

# rename variables to snake_space
data <- data |>
    mutate(SCD = ifelse(Group == "C-SCD",
        1, ifelse(Group == "C-Asthma", 0,
            NA)))

names(data) <- gsub("\\.\\.", "_", names(data))
names(data) <- tolower(gsub("\\.", "", names(data)))

data <- data |>
    rename(id = subjectid) |>
    select(-group) |>
    mutate(across(c(asthma, laba, ics, hydroxyurea),
        ~ifelse(. == "Yes", 1, ifelse(. ==
            "No", 0, NA))), gender = ifelse(tolower(gender) ==
        "female", 0, ifelse(tolower(gender) ==
        "male", 1, NA))  # Convert gender to lowercase before comparison
) |>
    filter(asthma == 1)


# mutate r5-20
data <- data |>
    mutate(r520hz_pp = r5hz_pp - r20hz_pp)
```

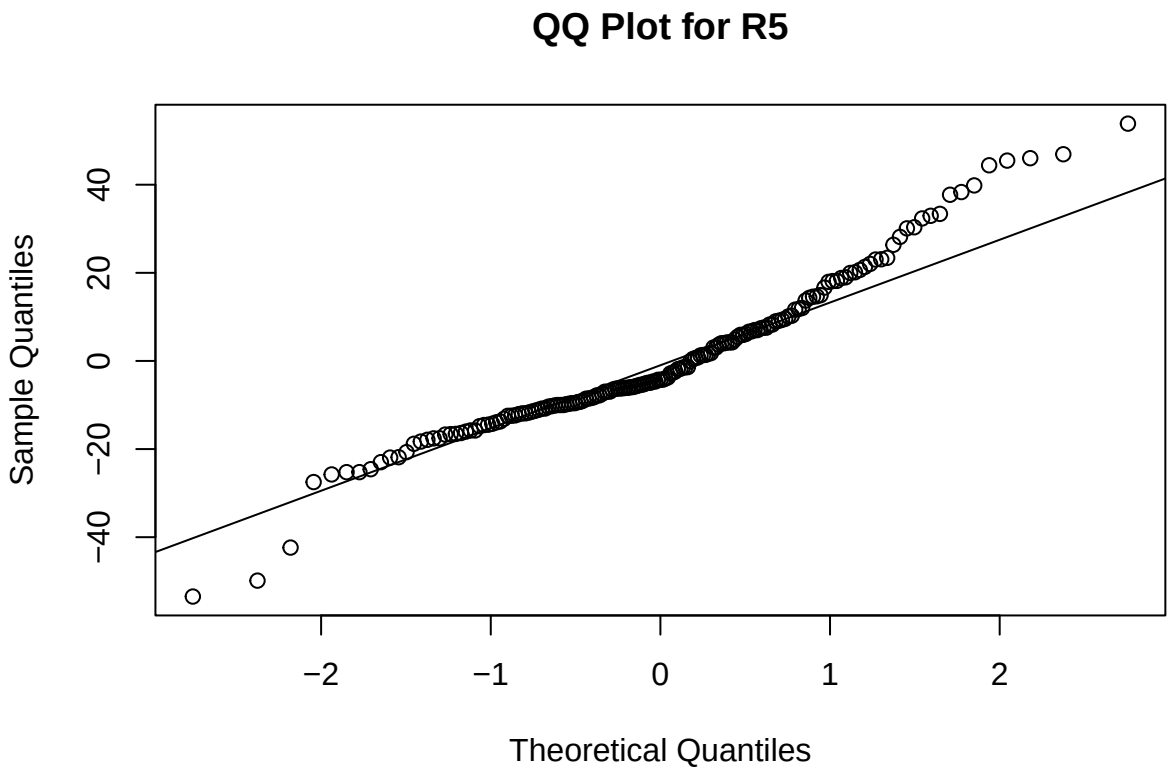
```r
# baseline summary statistics
baseline_df <- data |>
    group_by(id) |>
    filter(observation_number == min(observation_number)) |>
    ungroup()

summary(baseline_df)
```

```r
# show imbalanced feature
observation_counts <- data |>
    group_by(id) |>
    summarise(number_of_observations = n())

summary_of_observations <- observation_counts |>
    group_by(number_of_observations) |>
    summarise(ids_with_this_many_observations = n())

print(summary_of_observations)

# check consistance of variables

consistent_gender <- data |>
    group_by(id) |>
    summarise(n_distinct_gender = n_distinct(gender)) |>
    filter(n_distinct_gender > 1)
print(consistent_gender)
treatment_changes <- data |>
    group_by(id) |>
    summarise(n_distinct_ics = n_distinct(ics),
        n_distinct_laba = n_distinct(laba),
        n_distinct_hydroxyurea = n_distinct(hydroxyurea)) |>
    filter(n_distinct_ics > 1 | n_distinct_laba >
        1 | n_distinct_hydroxyurea > 1)
print(treatment_changes)

height_trends <- data |>
    arrange(id, age_months) |>
    group_by(id) |>
    mutate(height_change = c(NA, diff(height_cm))) |>
    summarise(downward_trend = all(height_change <
        0, na.rm = TRUE), num_observations = n()) |>
    filter(downward_trend == TRUE & num_observations >
        1)
```

```r
# plots
p1 = ggplot(data, aes(x = age_months, y = height_cm,
    group = id, color = factor(gender))) +
    geom_point() + geom_line() + scale_color_manual(values = c("#FA8072",
    "#56B4E9"), labels = c("Male", "Female")) +
    labs(title = "Relationship between Age and Height",
        x = "Age (months)", y = "Height (cm)",
        color = "Gender") + theme_minimal()
```

```r
p2 = ggplot(data, aes(x = age_months, y = bmi,
    group = id, color = factor(gender))) +
    geom_point() + geom_line() + scale_color_manual(values = c("#FA8072",
    "#56B4E9"), labels = c("Male", "Female")) +
    labs(title = "Relationship between Age and BMI",
        x = "Age (months)", y = "BMI", color = "Gender") +
    theme_minimal()

P1 = grid.arrange(p1, p2, ncol = 2)

p3 = ggplot(data, aes(x = age_months, y = r5hz_pp,
    group = id, color = factor(gender))) +
    geom_point() + geom_line() + scale_color_manual(values = c("#FA8072",
    "#56B4E9"), labels = c("Male", "Female")) +
    labs(title = "Relationship between Age and R5",
        x = "Age (months)", y = "R5", color = "Gender") +
    theme_minimal()

p4 = ggplot(data, aes(x = age_months, y = r20hz_pp,
    group = id, color = factor(gender))) +
    geom_point() + geom_line() + scale_color_manual(values = c("#FA8072",
    "#56B4E9"), labels = c("Male", "Female")) +
    labs(title = "Relationship between Age and R20",
        x = "Age (months)", y = "R5_20",
        color = "Gender") + theme_minimal()

p5 = ggplot(data, aes(x = age_months, y = r520hz_pp,
    group = id, color = factor(gender))) +
    geom_point() + geom_line() + scale_color_manual(values = c("#FA8072",
    "#56B4E9"), labels = c("Male", "Female")) +
    labs(title = "Relationship between Age and R5_20",
        x = "Age (months)", y = "R5_20",
        color = "Gender") + theme_minimal()

p6 = ggplot(data, aes(x = age_months, y = x5hz_pp,
    group = id, color = factor(gender))) +
    geom_point() + geom_line() + scale_color_manual(values = c("#FA8072",
    "#56B4E9"), labels = c("Male", "Female")) +
    labs(title = "Relationship between Age and X5",
        x = "Age (months)", y = "X5", color = "Gender") +
    theme_minimal()

p7 = ggplot(data, aes(x = age_months, y = fres_pp,
    group = id, color = factor(gender))) +
    geom_point() + geom_line() + scale_color_manual(values = c("#FA8072",
    "#56B4E9"), labels = c("Male", "Female")) +
    labs(title = "Relationship between Age and Fres",
        x = "Age (months)", y = "Fres", color = "Gender") +
    theme_minimal()

P2 = grid.arrange(p3, p4, p5, p6, p7, ncol = 3,
    nrow = 2)
```

```r
# exclude outliers
data_clean <- data |>
    mutate(across(c(r5hz_pp, r20hz_pp, x5hz_pp,
        fres_pp, r520hz_pp), ~ifelse(abs(scale(.)) >=
        3, NA, .)))

summary(data_clean)

# models
model_cr5 <- lmer(r5hz_pp ~ age_months +
    gender * bmi + scd + ics + laba + hydroxyurea +
    (1 | id), data = data_clean)

summary(model_cr5)
qqnorm(residuals(model_cr5), main = "QQ Plot for R5")
qqline(residuals(model_cr5))
```

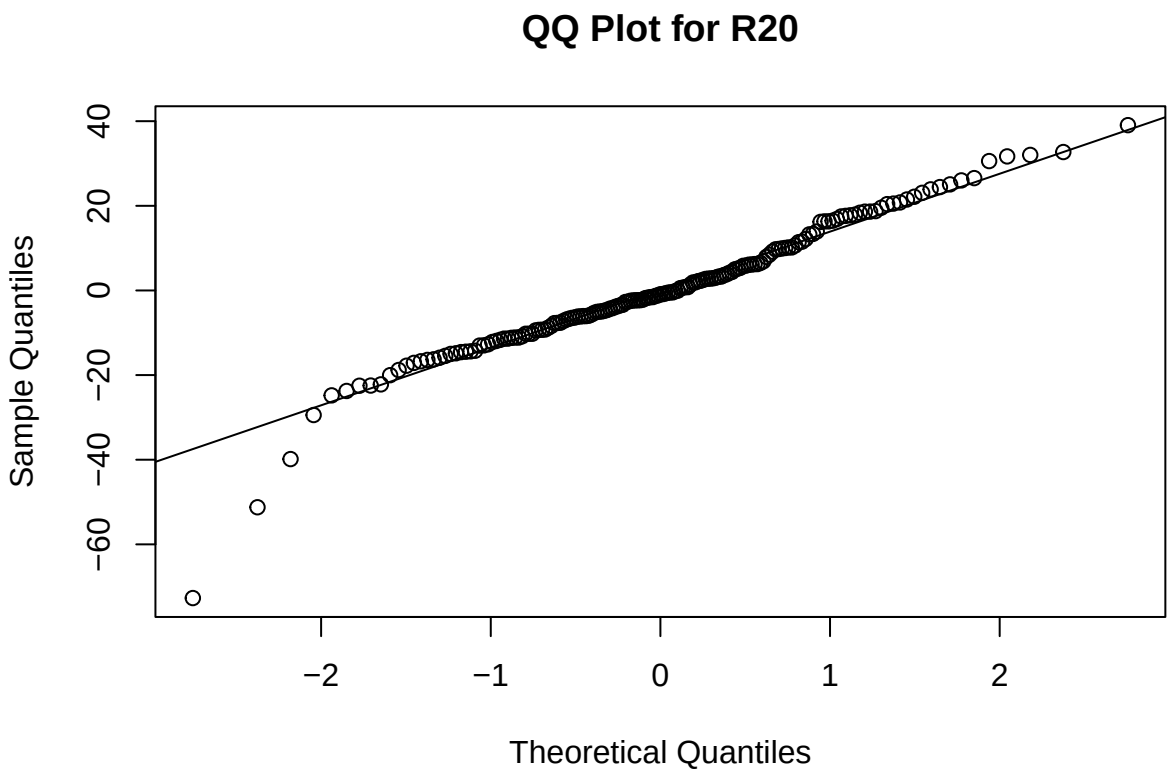



```r
confint(model_cr5, level = 0.95)
```

```
## Computing profile confidence intervals ...
```

```r
model_cr20 <- lmer(r20hz_pp ~ age_months +
    gender * bmi + scd + ics + laba + hydroxyurea +
    (1 | id), data = data_clean)
```

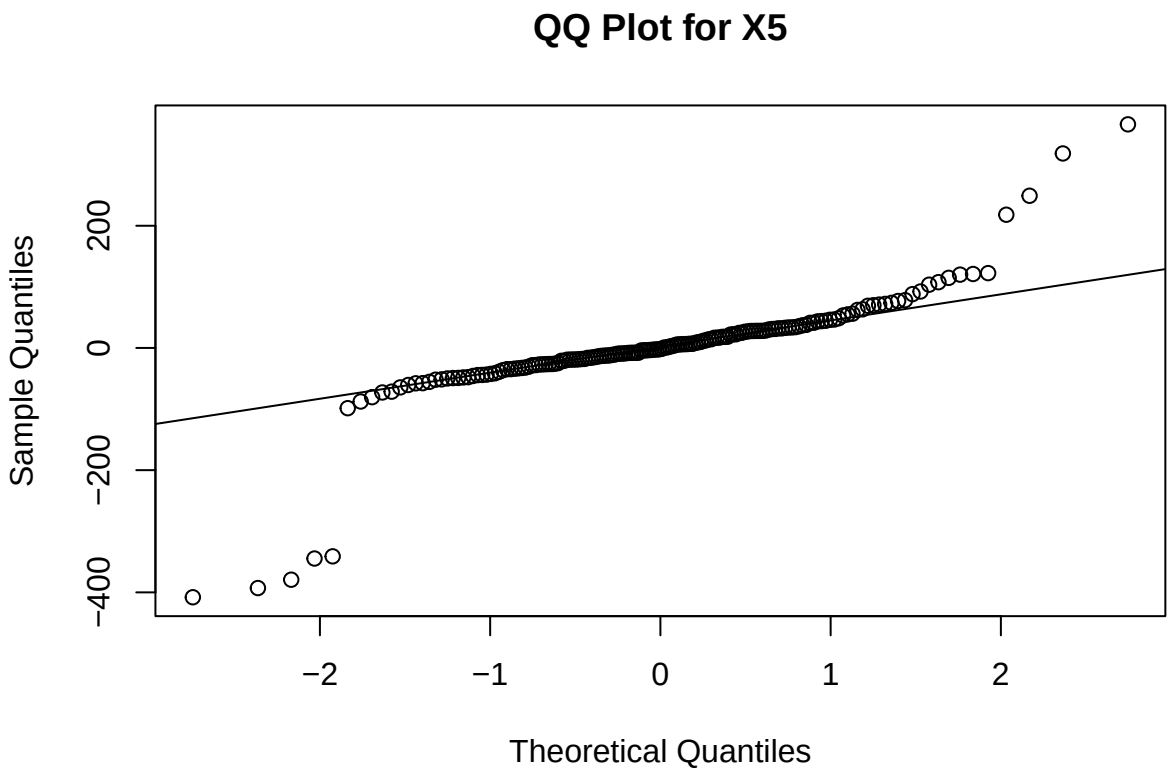
```
summary(model_cr20)
qqnorm(residuals(model_cr20), main = "QQ Plot for R20")
qqline(residuals(model_cr20))
```




```
confint(model_cr20, level = 0.95)
```

```
## Computing profile confidence intervals ...
```

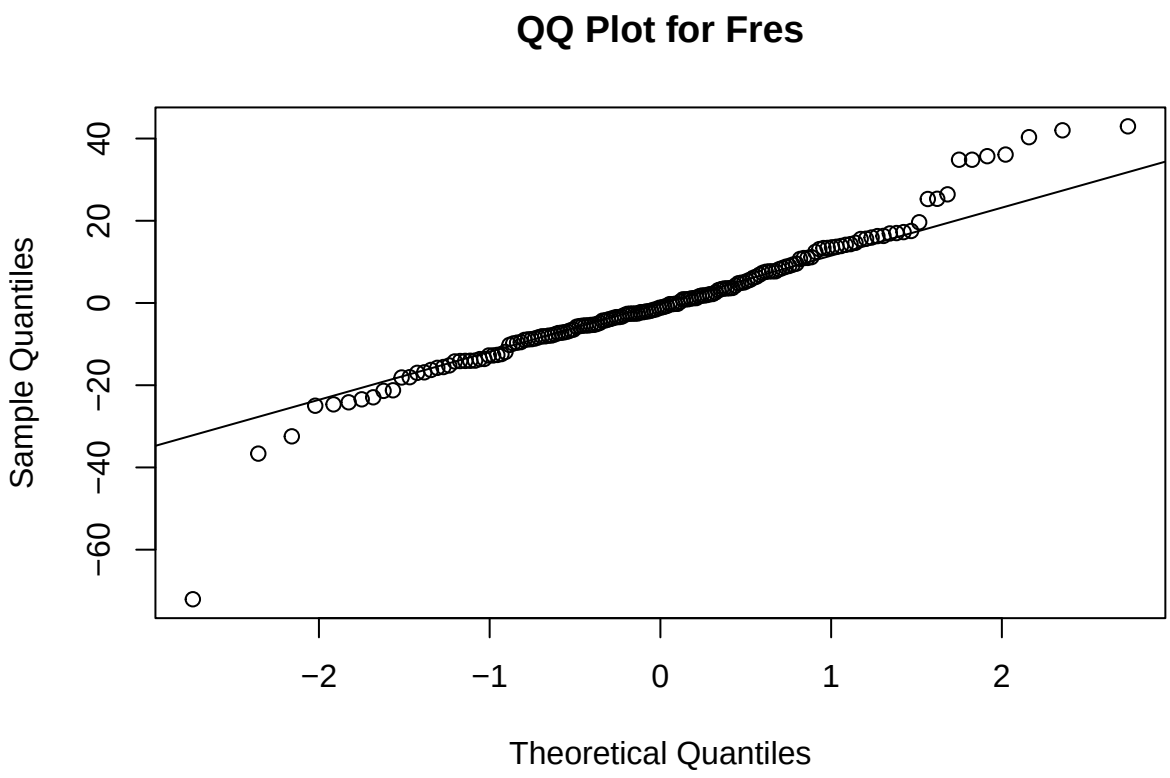
```
model_cx5 <- lmer(x5hz_pp ~ age_months +
    gender * bmi + scd + ics + laba + hydroxyurea +
    (1 | id), data = data_clean)

summary(model_cx5)
qqnorm(residuals(model_cx5), main = "QQ Plot for X5")
qqline(residuals(model_cx5))
```




```
confint(model_cx5, level = 0.95)
```

```
## Computing profile confidence intervals ...
```

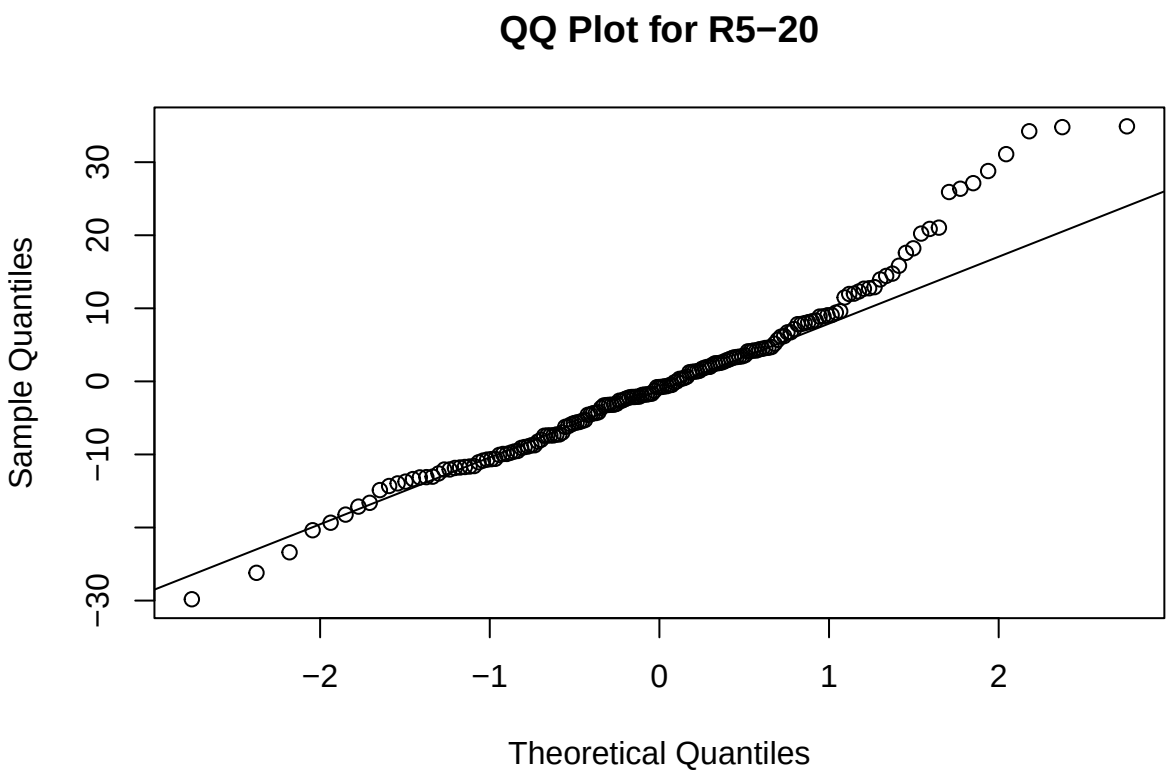
```
model_cfres <- lmer(fres_pp ~ age_months +
    gender * bmi + scd + ics + laba + hydroxyurea +
    (1 | id), data = data_clean)

summary(model_cfres)
qqnorm(residuals(model_cfres), main = "QQ Plot for Fres")
qqline(residuals(model_cfres))
```




```
confint(model_cfres, level = 0.95)
```

```
## Computing profile confidence intervals ...
```

```
model_cr520 <- lmer(r520hz_pp ~ age_months +
    gender * bmi + scd + ics + laba + hydroxyurea +
    (1 | id), data = data_clean)

summary(model_cr520)
qqnorm(residuals(model_cr520), main = "QQ Plot for R5-20")
qqline(residuals(model_cr520))
```




```
confint(model_cr520, level = 0.95)
```

```
## Computing profile confidence intervals ...
```