Statistical Analysis Report (SAR)

Title	Lung Function of Asthmatic Children and Presence of Pets
CRU/Department/Division/Center	Duke University, School of Medicine
Investigators:	Elizabeth Hauser
Biostatistician(s)	Caihan Wang
Original Creation Date	2021/4/29
Version Date	2021/4/30
Project Goal(s)	Test for association between lung function of asthmatic children and presence of pets
Submission Deadline(s)	2021/4/30

Investigator Agreement

☐ All statistical analyses included in an abstract or manuscript should reflect the work of the biostatistician(s) listed on this SAP. No changes or additional analyses should be made to the results or findings without discussing with the project biostatistician(s).
☐ All biostatisticians on this SAP should be given sufficient time to review the full presentation, abstract, manuscript, or grant and be included as co-authors on any abstract or manuscript resulting from the analyses.
☐ If substantial additional analysis is necessary or the aims of the project change, a new SAP will need to be developed.
☐ Publications resulting from this SAP are supported in part by the Duke CTSA and must cite grant number UL1TR002553 and be submitted to PubMed Central.
☐I have reviewed the SAP and understand that any changes must be documented.

Acknowledged by:
Date:

1. Study Overview

Asthma is a chronic condition of the lungs. For people who have asthma, their airways are constrict and may be filled with some mucus. Also, their breathing is difficult with wheezing, chest tightness, shortness of breath and coughing. Allergens and irritants in the air may trigger asthma symptoms and further exacerbate asthma. Additionally, childhood asthma may lead to impaired lung growth and impaired lung function in adulthood. So better control of asthma in childhood may lead to better lung function and lung growth. To control the asthma, people usually use bronchodilator, which could decrease resistance in the respiratory airway and increasing airflow to the lungs, including budesonide and nedocromil.

Asthma is a highly prevalent disease in US. It affects 25 million people, including 6.0 million children under 18. Therefore, it is very meaningful to study and explore the association of asthma in children. The main cause of asthma are allergens and irritants in the air, for example pet dander, smoke and so on. In this study, we mainly focus on whether the presence of pets at home is associated with lung function of children who have asthma.

1.1 Study Aims

1.1.1 Aim 1

To test the association between the presence of pets and decreased lung function at baseline, which measured by change in FEV1PP after bronchodilator in children with asthma

1.1.2 Aim 2

To test the association between the presence of pets and change in lung function from baseline to the last observation for each child, which measured by change in FEV1PP after bronchodilator in children with asthma

1.1.3 Aim 3

To test the association between the presence of pets and effects of treatment in children who are asthma, which measured by change in FEV1PP after bronchodilator form baseline to last observation for each child.

1.2 Study Hypotheses

1.2.1 Hypotheses 1

Null hypothesis: Presence of pets have no significant association with decreased lung function for children at baseline.

Alternative hypothesis: Presence of pets have significant association with decreased lung function for children at baseline.

1.2.2 Hypotheses 2

Null hypothesis: Presence of pets have no significant association with change in lung function from baseline to the last observation for each child.

Alternative hypothesis: Presence of pets have significant association with change in lung function from baseline to the last observation for each child.

1.2.3 Hypotheses 3

Null hypothesis: Presence of pets have no significant association with effects of treatment in children who are asthma.

Alternative hypothesis: Presence of pets have significant association with effects of treatment in children who are asthma.

2. Study Population

Our study used the data from Childhood Asthma Management Program (CAMP), which was a clinical trial carried out in children with asthma. The trial was designed to determine the long-term effects of 3 treatments (budesonide, nedocromil, or placebo) on pulmonary function as measured by normalized FEV1 over a 5-6.5 year period. CAMP consists of 1,041 children (311 in the budesonide group, 312 in the nedocromil group and 418 in the placebo group) aged 5-12 years and enrolled between December of 1993 and September of 1995. As for our study population, we used data of 695 children in “camp_teach.csv”, which came from CAMP.

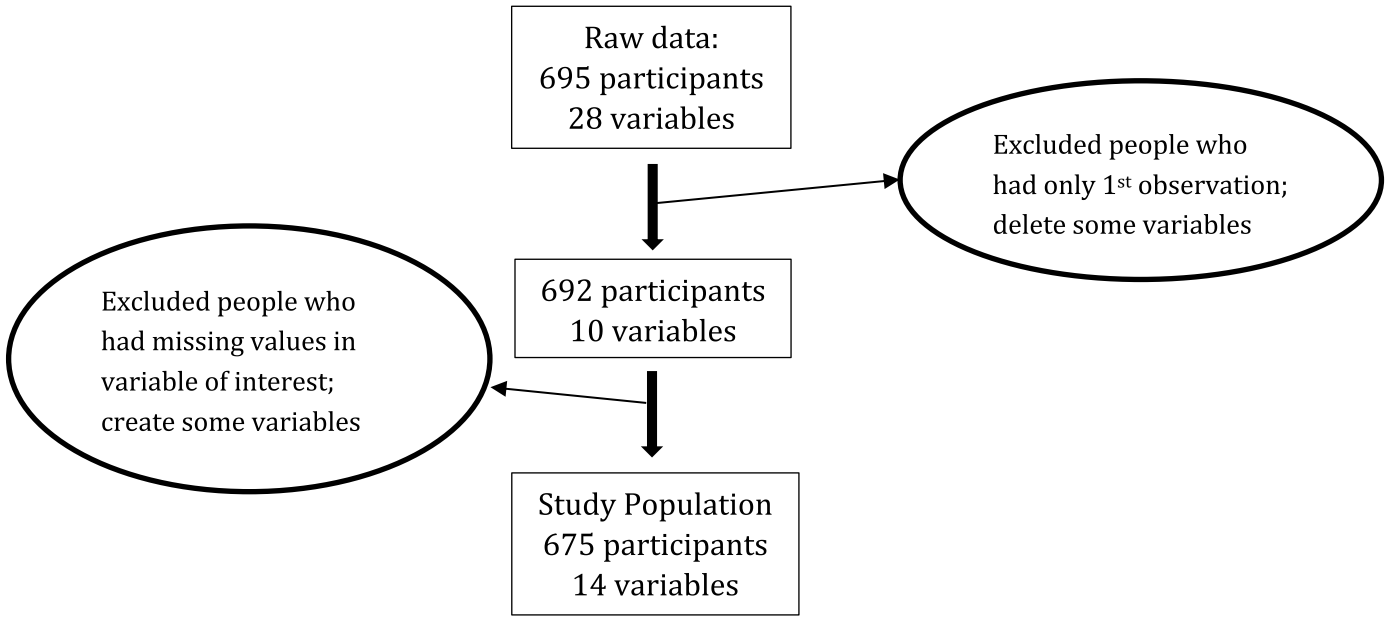
2.1 Inclusion Criteria

- All participants’ data in baseline and last observation (number = 695)

2.2 Exclusion Criteria

- Participants who only had first observation (number = 3)
- Participants who had missing values in variable of interest (number = 17)

2.3 Flow Chart for Inclusion & Exclusion



2.4 Data Acquisition

Fill in all relevant information:

Study design	Retrospective study
Data source/how the data were collected	Childhood Asthma Management Program
Contact information for team member responsible for data collection/acquisition	Elizabeth.hauser@duke.edu
Date or version (if downloaded, provide date)	April 29, 2021
Data transfer date	April 29, 2021
Where dataset is stored	Duke University Sakai

Description: Our data comes from Childhood Asthma Management Program. A total of 1,041 children (311 in the budesonide group, 312 in the nedocromil group and 418 in the placebo group) aged 5-12 years were enrolled between December of 1993 and September of 1995. We used data of 695 children in CAMP, and after data cleaning, the number of people finally included in the analysis is 675.

3. Outcomes, Exposures, and Additional Variables of Interest

3.1 Outcome(s) for aim 1

Outcome	Description	Specifications
Lung_Func_base	Lung function in baseline, measured by change in FEV1PP after bronchodilator	Continuous variable ranging from -15 to 42; mean is 9.23; standard deviation is 7.32

3.2 Outcome(s) for aim 2

Outcome	Description	Specifications
Lung_Func_diff	Difference of lung function between baseline and last observation of each children, measured by change in FEV1PP after bronchodilator in children with asthma.	Continuous variable ranging from -45 to 31; mean is -2.01; standard deviation is 8.16

3.3 Outcome(s) for aim 3

Outcome	Description	Specifications
Trt_Effects	The effects of treatment, mesasured by change in FEV1PP after bronchodilator from baseline to last observation for each child. (Post of FEV1PP in last observation minus post of FEV1PP in baseline)	Continuous variable ranging from -37 to 51; mean is 0.98; standard deviation is 11.96

3.4 Additional Variables of Interest

Variable	Description	Specifications
id	Randomized participant ID	Integer ranging from 1 to 1041
age_rz	Age in years at Randomization	Continuous variable ranging from 5 to 13; mean is 8.35; standard deviation is 2.13
GENDER	Gender of the children	m = male; f = female
ETHNIC	Ethnic of the children	w = white, b = black, h = hispanic, o = other
TG	Treatment groups	A = bud, B = ned, C = plbo
anypet	Presence of pet at home	1 = Yes; 0 = No

3.5 Demographic Table

	with pet	without pet	Total
Total	475	200	675
Gender			
Male	286	116	402
Female	189	84	273
Ethnic			
White	329	137	466
Black	59	27	86
Hispanic	42	23	65
Other	45	13	58
Treatmet Groups			
bud	142	61	203
ned	147	56	203
plbo	186	83	269
Age at Randomization			
5~9	310	143	453
10~13	165	57	222

Table 1. Demographic Table

4. Statistical Analysis Plan

To achieve our study aims, we choose multiple linear regression model and two-way ANOVA model to investigate the association of lung function at baseline and presence of pet, lung function change from baseline to last observation and presence of pet, treatment effects and presence of pet. In order to measure the lung function, we choose to calculate change in FEV1PP after bronchodilator in children with asthma. In order to measure the treatment effects, we choose to calculate the change in FEV1PP after bronchodilator from baseline to last observation for each child, which means post of FEV1PP in last observation minus post of FEV1PP in baseline.

In addition, in order to describe the distribution of outcome variables (Lung_Func_base, Lung_Func_diff, Trt_Effects), we choose to use histograms to show their rough distribution. And then, we draw their corresponding qq-plot, which could show their distribution specifically.

4.1 Analysis Plan for Aim 1

To test the association between the presence of pets and decreased lung function at baseline, we will fit a multiple liner regression model as following:

$$Lung\_Func\_base = \beta_{0a} + \beta_{1a}(anypet) + \beta_{2a}(age\_rz) + \beta_{3a}(GENDER) + \beta_{4a}(ETHNIC) + \varepsilon_a$$

------(Model 1)

The independent variables consist of not only anypet, which we are mainly concerned with, but also age at randomization, gender and ethnic, because these variables reflect the basic situation of the patient. The dependent variable is lung function at baseline for asthmatic children.

For testing the p-value of parameters in this multiple liner regression model, we set the significant level at 5%. The coefficients with p-value less than 0.05 will be considered as significant. In this case, if the p-value of anypet term is less than 0.05, we will conclude that there is a strong association between the presence of pets and decreased lung function at baseline. And then, we will also draw a plot to better visualize the model.

4.2 Analysis Plan for Aim 2

To test the association between the presence of pets and change in lung function from baseline to the last observation for each child, we will fit a multiple liner regression model as following:

$$Lung\_Func\_diff = \beta_{0b} + \beta_{1b}(anypet) + \beta_{2b}(age\_rz) + \beta_{3b}(GENDER) + \beta_{4b}(ETHNIC) + \varepsilon_b$$

------(Model 2)

Similarly, the independent variables consist of not only anypet, which we are mainly concerned with, but also age at randomization, gender and ethnic. The dependent variable is lung function difference between baseline and last observation for asthmatic children.

For testing the p-value of parameters in this multiple liner regression model, we set the significant level at 5%. The coefficients with p-value less than 0.05 will be considered as significant. In this case, if the p-value of anypet term is less than 0.05, we will conclude that there is a strong association between the presence of pets and lung function change from the first observation to the last observation for asthmatic children. And then, we will also draw a plot to better visualize the model.

4.3 Analysis Plan for Aim 3

To test the association between the presence of pets and effects of treatment in children who are asthma, we cannot ignore the influence of treatment group. As we can see in the following boxplot, this is a boxplot of treatment effects group by treatment group and presence of pet. It is possible that treatment group is a confounder or have some interaction with presence of pet. Therefore, we will take this variable into account.

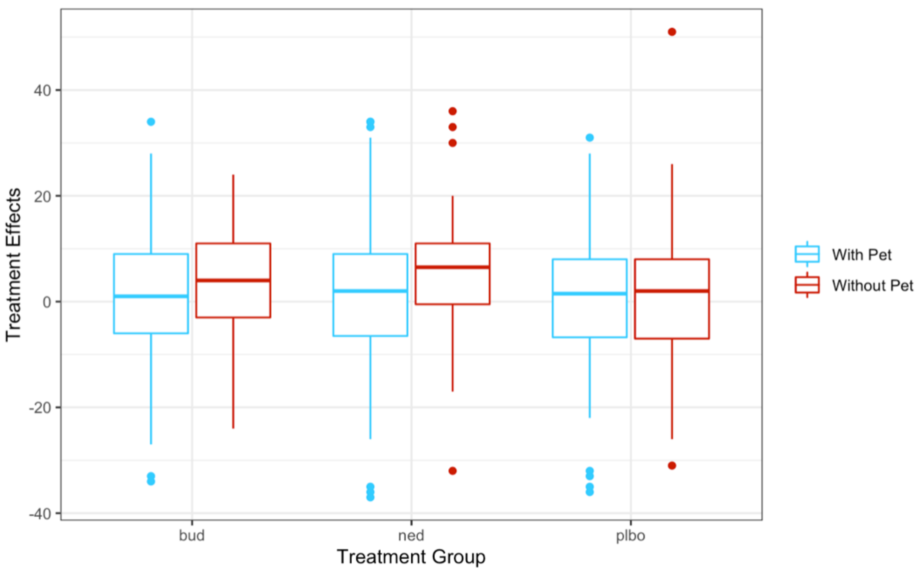


Figure 1. Boxplot of Treatment Effects

So we will fit a two-way ANOVA model as following:

$$Trt\_Effects = \mu_{..} + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \epsilon \text{------(Model 3)}$$

The independent variables consist of presence of pet and treatment group. The dependent variable is treatment effects calculated between baseline and last observation for asthmatic children.

For testing the p-value of parameters in this two-way ANOVA model, we set the significant level at 5%. The coefficients with p-value less than 0.05 will be considered as significant. In this case, if the p-value of anypet term is less than 0.05, we will conclude that there is a strong association between the presence of pets and treatment effects. And then, we will also draw a plot to better visualize the model.

5. Statistical Analysis Result

5.1 Distribution of Outcome variables

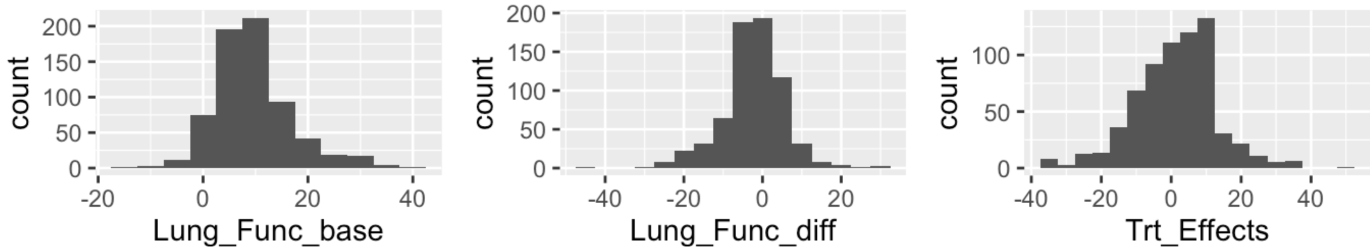


Figure 2. Histograms of Lung Function, Lung Function Difference and Treatment Effects

As we can see in the figure 2, the above three histograms are very close to the normal distribution. To further verify our conjecture, the qq-plots of each variable are as following:

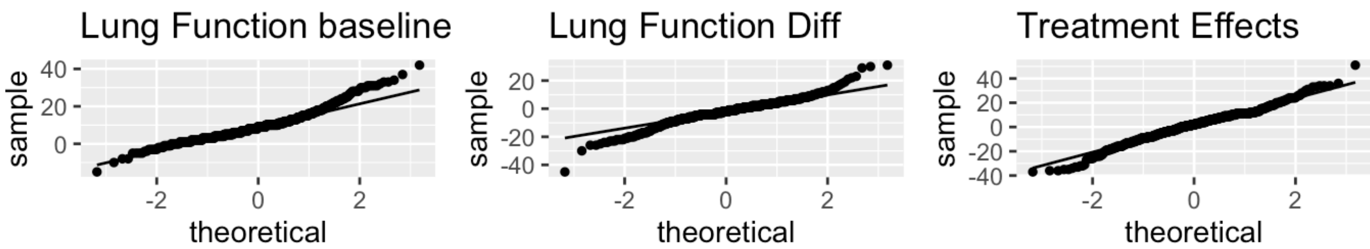


Figure 3. QQ-plots of Lung Function, Lung Function Difference and Treatment Effects

Therefore, according to the above two figures, the distributions of Lung Function at Baseline, Lung Function Difference and Treatment Effects are normal distribution. Specifically, Lung Function at Baseline follows a normal distribution with a mean of 9.23 and standard deviation of 7.32. Lung Function Difference follows a normal distribution with a mean of -2.01and standard deviation of 8.16. Treatment Effect follows a normal distribution with a mean of 0.98 and standard deviation of 11.96. Since they are all normal distribution, we can use them as dependent variables to construct the multiple liner regression models and two-way ANOVA model.

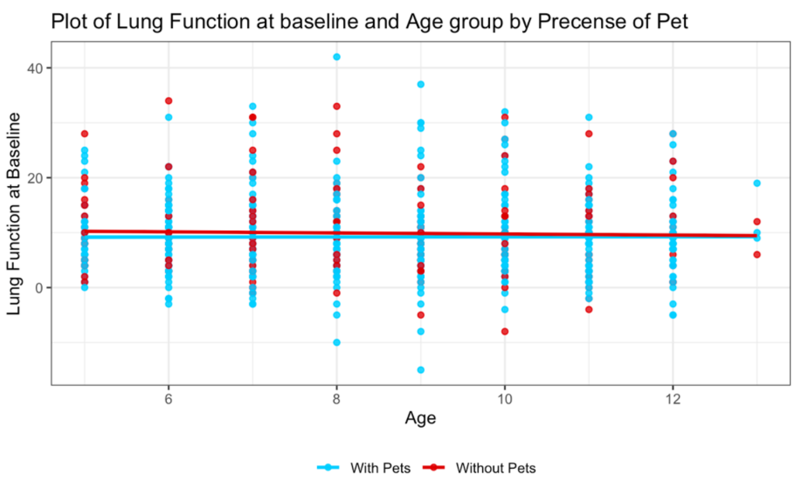
5.2 Statistical Analysis Result for Aim 1

```
glm(formula = Lung_Func_base ~ factor(anypet.x) + age_rz.x +
    factor(GENDER.x) + factor(ETHNIC.x), family = gaussian, data = ds4)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-24.113   -4.839   -0.723    3.344   32.891

Coefficients:
                  Estimate Std. Error t value Pr(>|t|)
(Intercept)       10.01195    1.46693   6.825 1.97e-11 ***
factor(anypet.x)2  0.69337    0.61989   1.119    0.264
age_rz.x          -0.02891    0.13266  -0.218    0.828
factor(GENDER.x)m -0.38182    0.57822  -0.660    0.509
factor(ETHNIC.x)h -0.63907    1.20846  -0.529    0.597
factor(ETHNIC.x)o -0.77305    1.24733  -0.620    0.536
factor(ETHNIC.x)w -0.28959    0.86112  -0.336    0.737
```

Figure 4. Result of Model 1

The left figure is the calculation result of the Model 1 (liner regression model). The result indicates that the association between anypet and lung function is not significant because p-values of this term is more than 0.05. Therefore, Presence of pet and lung function at baseline for asthmatic children have no significant association.

The right figure following is the visualization of the Model 1. As we can see, there is no significant difference of lung function at baseline between people with pet and people without pet.



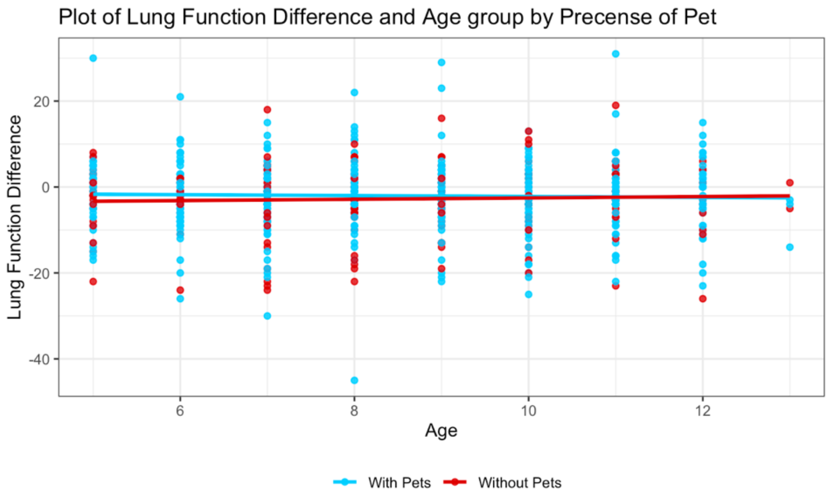
5.3 Statistical Analysis Result for Aim 2

```
glm(formula = Lung_Func_diff ~ factor(anypet.x) + age_rz.x +
    factor(GENDER.x) + factor(ETHNIC.x), family = gaussian, data = ds4)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-43.130   -3.453    0.591    4.718   32.925

Coefficients:
                  Estimate Std. Error t value Pr(>|t|)
(Intercept)       -1.94206    1.60561  -1.210    0.227
factor(anypet.x)2 -0.83320    0.67850  -1.228    0.220
age_rz.x          -0.01829    0.14520  -0.126    0.900
factor(GENDER.x)m -0.13771    0.63288  -0.218    0.828
factor(ETHNIC.x)h  0.24751    1.32270   0.187    0.852
factor(ETHNIC.x)o -1.34663    1.36525  -0.986    0.324
factor(ETHNIC.x)w  0.35623    0.94253   0.378    0.706
```

Figure 5. Result of Model 2

The figure on the left is the calculation result of Model 2. The result indicates that association between anypet and lung function change from the first to the last observation is not significant because p-values of this term is more than 0.05. Therefore, Presence of pet and lung function difference from baseline to last observation for asthmatic children have no significant association.

The right figure is the visualization of the Model 2. As we can see, there is no significant difference of lung function change from baseline to last observation between people with pet and people without pet.



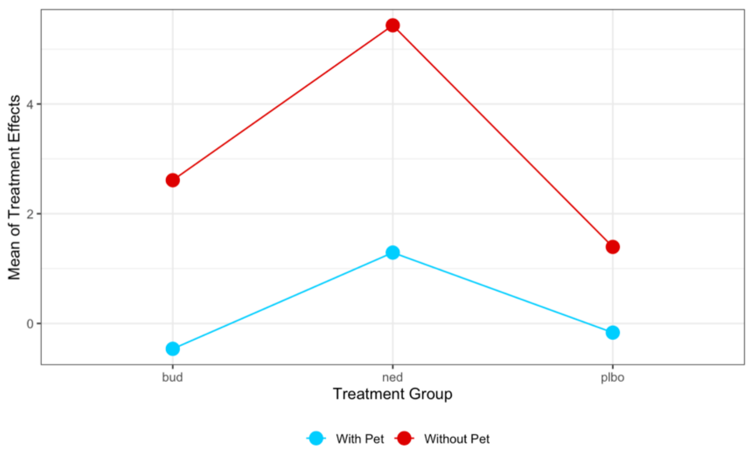
5.4 Statistical Analysis Result for Aim 3

```
Response: Trt_Effects
                              Df Sum Sq Mean Sq F value Pr(>F)
factor(anypet.x)               1    872  872.24  6.3152 0.0122 *
factor(TG.x)                   2    383  191.58  1.3871 0.2505
factor(anypet.x):factor(TG.x)  2    290  145.07  1.0503 0.3504
Residuals                    669  92401  138.12
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 7. Result of Model 3

The figure on the left is the calculation result of Model 3 (Two-way ANOVA). The result indicates that association between anypet and treatment effects is significant because p-values of this term is less than 0.05. Therefore, Presence of pet and treatment effects have a significant association. However, the P-value of treatment group is less than 0.05, which means that these three treatment groups have the same treatment effects. Also, the interaction term is not significant, which means there is no interaction between presence of pet and treatment groups.

The right figure is the visualization of the Model 3. As we can see, there is a significant difference of treatment effects between people with pet and people without pet. To be more specific, people without pet can get better treatment effects than those with pet. Also, because these two lines are roughly paralleled, there is no interaction between treatment groups and presence of pets.



6. Interpretation & Discussion of Results

According to our statistical results, we can conclude that children's lung function and lung function change have no association with presence of pets. However, as for treatment effects, children without pet could have better treatment effects than those with pet. Therefore, for family with asthmatic children, we highly recommend them not to keep pets, which could help their children get better treatment effects.

There are also some limitations of our study. The sample size is not large enough and the numbers of children with and without pet are unbalanced. Also, the status of keeping pets can change during the whole period, which will also cause some biases on our results.

7. References

1. https://www.nhlbi.nih.gov/health-topics/asthma
2. The Childhood Asthma Management Program Research Group (2000). Long-term Effects of Budesonide and Necrodomil in Children with Asthma. JAMA 343 (15): 1054-1063.
3. Howrylak J et al. (2014). Cotinine in Children Admitted for Asthma and Readmission. Pediatrics 133 (2): e355-
4. Apelberg BJ, Aoki Y, Jaakkola JJK (2001) Systematic review: Exposure to pets and risk of asthma and asthma-like symptoms. J Allergy Clin Immunol 107(2): 455-460.

8. Appendix

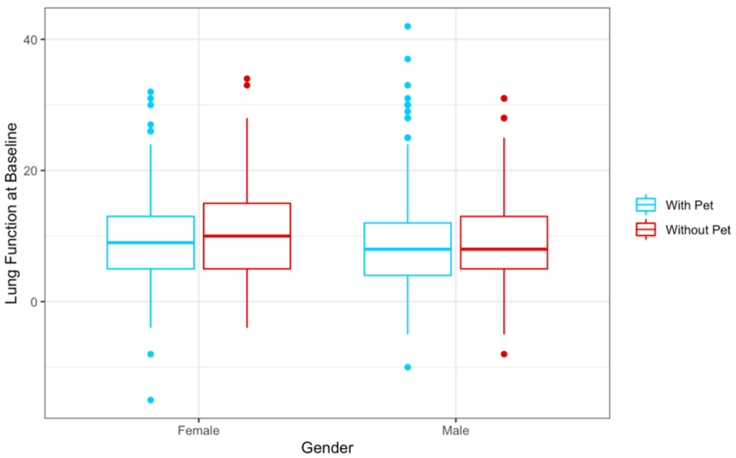


Figure 8. Boxplot of Lung Function by pet and sex

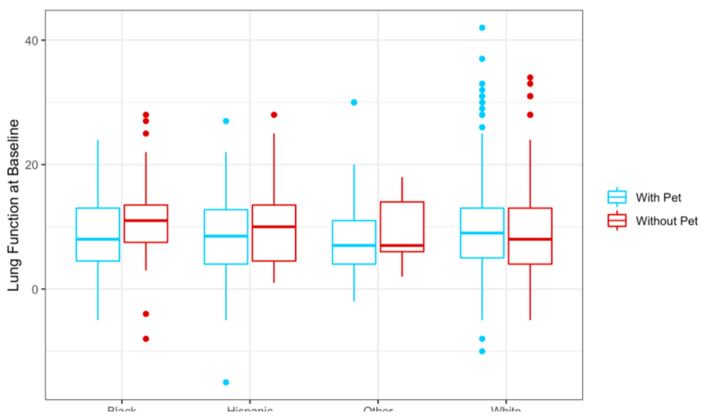


Figure 9. Boxplot of Lung Function by Ethnic and Pet