Adding Exhaled Nitric Oxide to Guideline-based Asthma Treatment in Inner-City Adolescents and Young Adults : A Randomized Controlled Trial

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SDY210 Introduction

The study aim is to determine whether measurement of exhaled NO(eNO) could increase the effectiveness of asthma treatment. (Asthma guideline vs. Asthma guideline + eNO)
Study participants will get through 8 visits in total for every 6-8 weeks.

Asthma Treatment Guideline

1.
2.
3.
4.
5.

vs.

Asthma Treatment Guideline + eNO

1.
2.
3.
4.
5.
6. **eNO measurement**

From Wk1 to Wk3
Run-in period ("Irrigation")

1 — 2 — 3 — 4

Visit 1
- Enrollment
- Baseline check

After Run-in
- Block Randomization
- Standard treatment

Visit 8
- Final study visit

8 — 7 — 6 — 5

From Visit 2 to Visit 8 (46 weeks of follow up)
For each visit, physicians assess patients by asking asthma symptom-related questions.

Study Design

- Randomized, Double-blinded, parallel-group **clinical trial**
- **longitudinal study** lasting for 46 weeks & **multi-center** study: 10 inner cities
- People of interest:
    - 12 to 20 years old male and female **adolescents**
    - Excluded bottom 20% of households income (i.e. below poverty line)
    - Diagnosis of asthma by physician before
- Outcomes :
    - **Primary** : asthma symptom days, lung function, unscheduled visits, hospitalization, Corticosteroid
    - **Secondary** : hospitalizations, unscheduled visits, prednisone use, and exacerbations

Sample Size Calculation & Randomization

The study recruited 780 subjects, and only 546 subjects were left after screening and drop-out. Also, after run-in period, they applied centralized block randomization.

```
> pwr.t.test(p = 0.9,
             d = 0.7/2.4,
             sig.level = 0.05,
             type = "two.sample")
[1] 496
```

- Used **`pwr::pwr.t.test`** function
- Obtained 496 as a required sample size
- 764 subjects required at 35% drop-out rate

stratum	block.id	block.size	treatment
site 1	1	4.000	eNO
site 1	1	4.000	control
site 1	1	4.000	control
site 1	1	4.000	eNO
site 1	2	14.000	eNO

- Used **`blockrand::blockrand`** function
- Centralized block randomization
  - Block size: 10
  - Randomization sequence generated from random number table

Study Objectives

Primary Outcome

- To evaluate if the biomarker(eNO) supplemented approach to asthma therapy improves asthma outcomes as compared to a guidelines-based approach without the use of a specific biomarker.

Secondary Outcome

- Asthma-related use of health care
    - e.g. Admission to hospital, Unscheduled use of health care, Prednisone course, Exacerbation, and etc.

Additional Sub-Group Analysis

- Based on the results of the primary objective, a subgroup analysis will be performed on only male participants.

Data Exploration - Table1

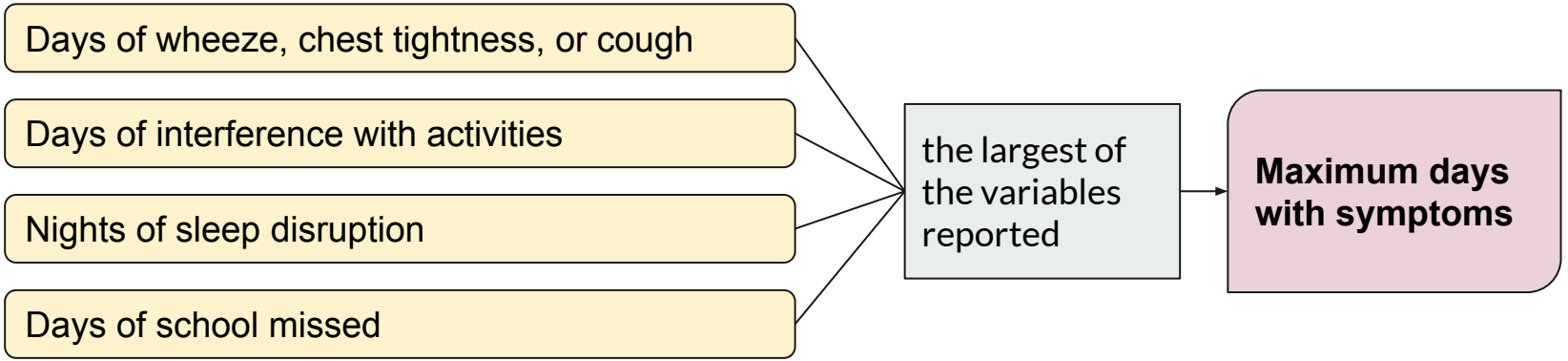
The result matched with the result of the study.

- Demographic characteristics of participants in the two treatment groups did not differ.
- Compared with pre-study levels, asthma-related symptoms alleviated over the run-in period

	All participants at enrolment (n=546)	Treatment Group (n=276)	Control Group (n=270)
Demographic characteristics			
Age at recruitment (years)	13.89(1.78)	13.88(1.76)	13.9(1.81)
Sex (male)	288/546 (53%)	146/276 (53%)	142/270 (53%)
Ethnic origin			
Black	356/546 (65%)	184/276(67%)	172/270(64%)
Hispanic	148/546 (27%)	69/276(25%)	79/270(29%)
Other or mixed	42/546 (7%)	23/276(8%)	19/270(7%)
Household income <US$15 000	151/502(30%)	70/251(28%)	81/251(32%)
Asthma-related characteristics			
Days with asthma-related symptoms			
Maximum days with symptoms	5.8(4.7)	2.2(2.8)	2.5(3.0)
Days of wheeze, chest tightness, or cough	4.5(4.1)	1.8(2.7)	2.2(3.0)
Days of interference with activities	3.3(4.1)	1.2(1.9)	1.0(1.7)
Nights of sleep disruption	2.7(3.7)	0.6(1.5)	0.6(1.4)
Days of school missed	0.7(1.4)	0.2(0.6)	0.3(1.0)
Use of asthma-related health care in the year before enrolment			
≥1 admission to hospital	51/546	26/276	25/270
≥1 unscheduled visit	99/546	47/276	52/270
≥1 prednisone course	197/546	93/276	104/270
≥1 exacerbation	249/546	121/276	128/270

Primary Outcome - Method

1) **Variable explanation**



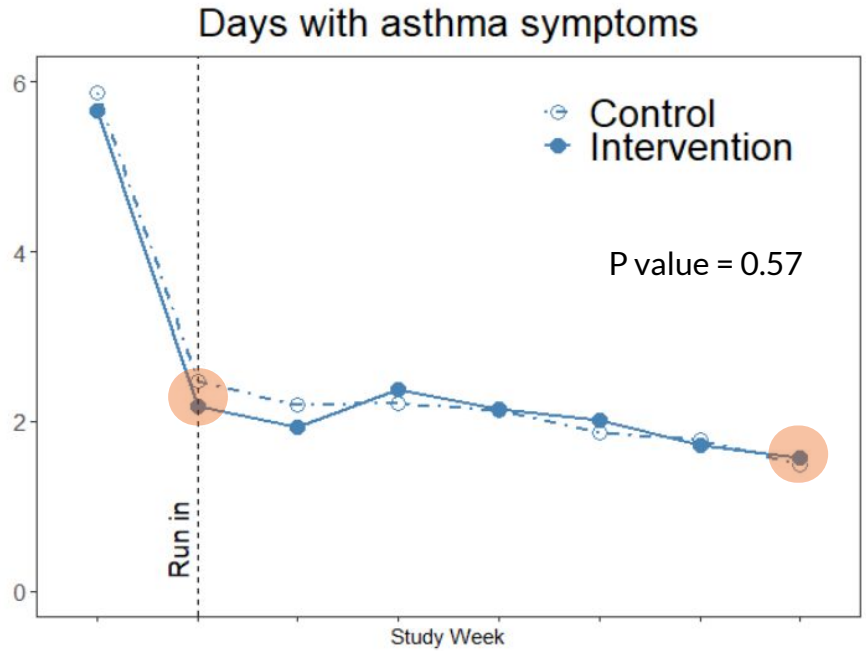
2) **ANCOVA Model**

- In clinical trials, the outcome often is affected by not only the treatments but also other covariates, especially **the pretreatment/baseline value of the outcome variable**

$$y\_post \sim treatment + y\_pre$$

Primary Outcome - Result

This treatment option did not produce an overall improvement in asthma symptoms.



- **Pre-treatment outcome measurement**
  Maximum days with symptoms at Visit 2
- **Post-treatment outcome measurement**
  Maximum days with symptoms at Visit 8:

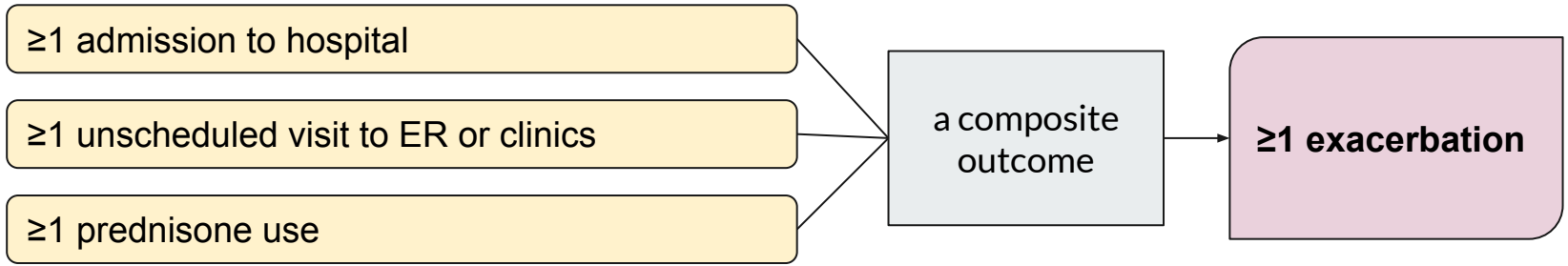
Model : max_v8 ~ max_v2 + Treatment

- Baseline is significant (p value < 0.001)
- Treatment is not significant (p value = 0.57)

Secondary Outcome - Method

Variable explanation

- Rare event, Asthma-related use of health care
- Summed the events over the course of the study
- Binary outcome : 'any' versus 'none'

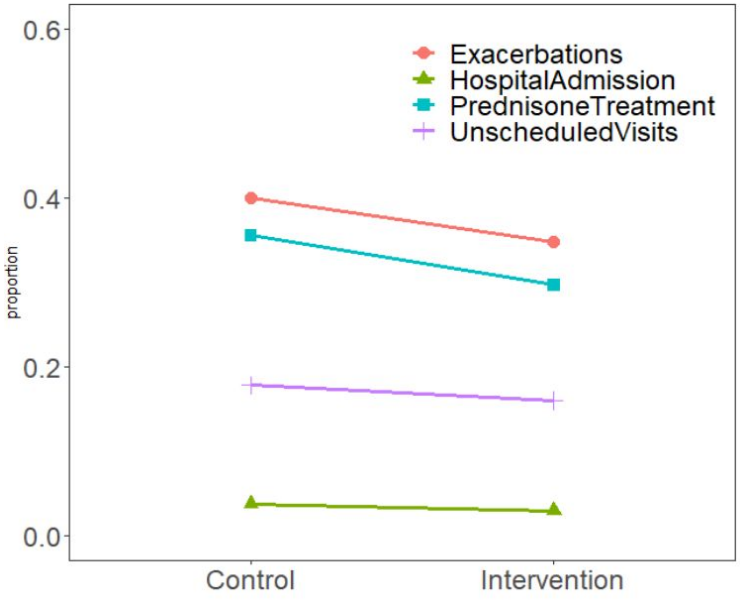


2) Method

- Compare the **proportions** (probability of rare events happens) between intervention v.s. Control group

Secondary Outcome - Result

Overall use of health care was low and didn't differ between the groups.

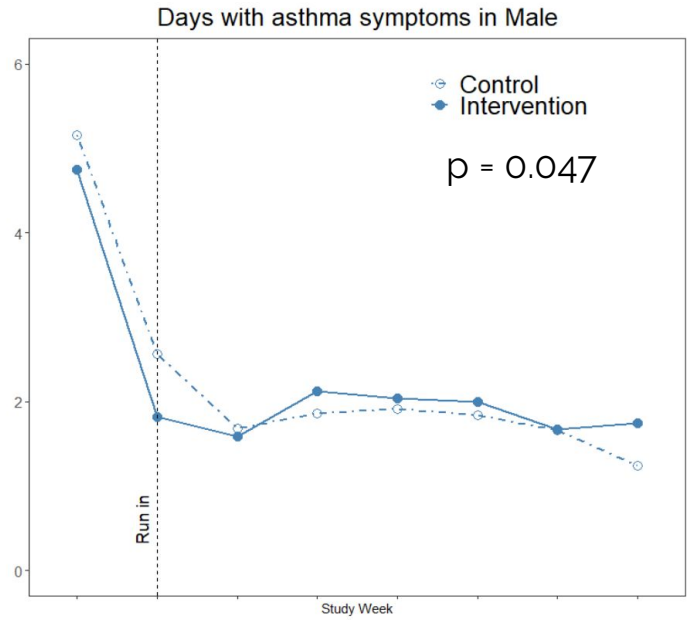


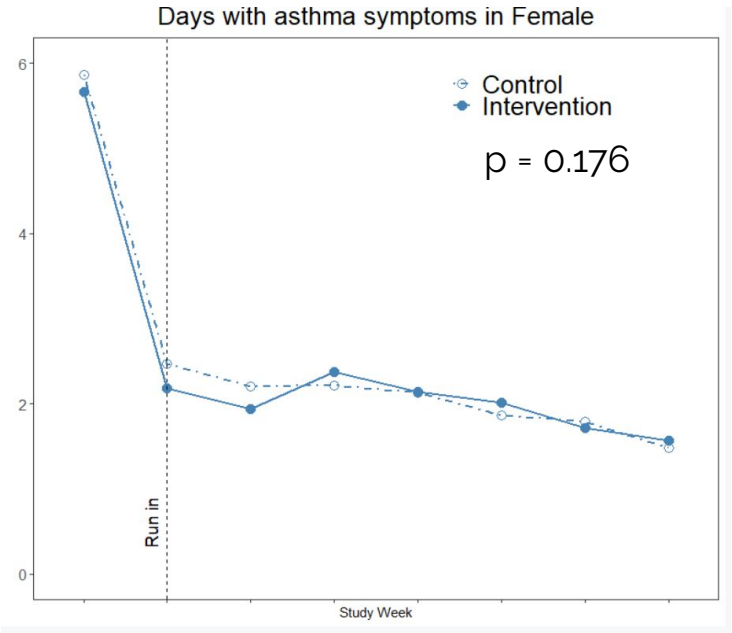
	No-monitoring group (n=276)	Control (n=270)	Diff	p-val
Asthma-related use of health care throughout the study				
≥ 1 admission to hospital	2.9%	3.7%	-0.8%	0.60
≥ 1 unscheduled visit	15.9%	17.8%	-1.8%	0.57
≥ 1 prednisone course	29.7%	35.6%	-5.8%	0.15
≥ 1 exacerbation	34.8%	40.0%	-5.2%	0.21

* Chi-square test was used to generate p-values.

Subgroup of Interest - Male vs. Female

Stratified the data by obesity, race, Income, or gender. The result showed that there is a significant treatment effect in male (β = .63, p = 0.047)





Discussion & Conclusion

Conventional asthma management guideline resulted in good control of symptoms in most participants.

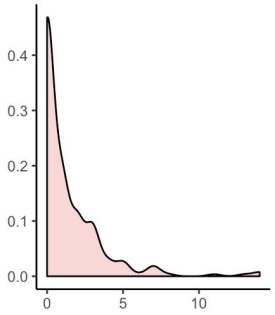
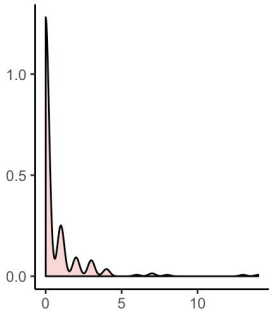
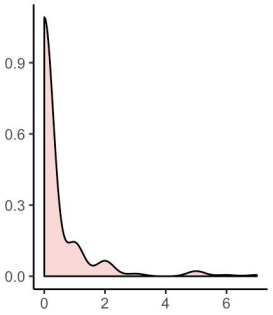
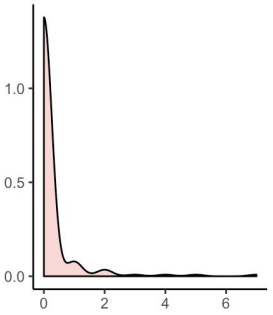
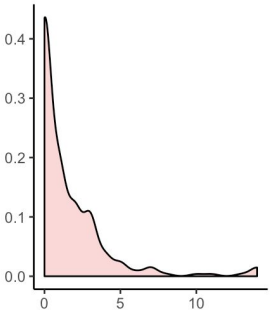
Conclusion

- **Primary:** no significant difference in treatment effect was shown between eNO group and the control.
- **Secondary:** Out of four variables (hospitalizations, unscheduled visits, prednisone use, and exacerbations), none of them showed significant results.
- **Sub-group analysis:** significant difference in primary outcome in male ($p = 0.047$)

Limitations

- ANCOVA model may be not enough to meet the assumptions.
  - Using linear mixed model looks more appropriate.
  - However, there are some missing variables that prevents us from reproduction.
  - e.g. Adjustment for region, but blinded due to privacy issue (even state level)

Appendix: Continuous Variable

	Days of Wheeze	Days of Interference with Activities	Nights of Sleep Disruption	Days of School Missed	Maximum Days With Symptoms
eNO					
Control