Modification of Treatment Efficacy in Asthma Clinical Trials by Social and Environmental Co-exposures

Lizbeth Gómez[1], Ellen Kinnee[2], Michael T. Young[4], Joel Kaufman[4], Fernando Holguin[3], Dave Mauger[5], Jane E. Clougherty[1]

[1]Drexel University Dornsife School of Public Health, [2]University of Pittsburgh Graduate School of Public Health, [3]University of Colorado Denver School of Medicine, [4]University of Washington School of Public Health, [5]Department of Public Health Sciences, Penn State University

Background

- Substantial evidence links air pollution and socioeconomic position (SEP) to asthma outcomes[1,2].
- Randomized clinical trials (RCTs) are the standard of evidence in medical research, as randomization balances measured and unmeasured confounders, promotes homogeneity of participant characteristics across study arms, and maximize internal validity.
- Few RCTs, however, have considered whether treatment efficacy may be modified by social and environmental co-exposures.

Aims

- To evaluate whether air pollution and SEP indicators predict asthma outcomes, or altered observed treatment efficacy in an asthma RCT.
- To test, using Cox proportional hazard models, whether treatment effects on time-to-prednisone-use (an asthma severity measure) differs by NO_2, $PM_{2.5}$, O_3, or SEP indicators.

Methods

- Secondary analysis of AsthmaNet's Step-up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations (STICS) trial.
- Participants (n=219) were randomly assigned to low vs. high dose (44 vs. 220 µg/inhalation) of fluticasone inhaled corticosteroid (ICS) treatment at exacerbation onset, then followed to assess subsequent exacerbations (Fig 2A).
- We geocoded participant's residences, estimated NO_2, $PM_{2.5}$, and O_3 using national universal kriging models,[4] assigned Census Block poverty rates, and medically underserved areas (MUAs) (Fig 1)].
- Used Cox proportional hazard models to assess time-to-prednisone use by treatment arm, by social and environmental co-exposures - adjusting for race/ethnicity, household income, parental smoking, body mass index (BMI), number of household pets, and city/ recruitment site.

Figure 1: Exposure assessment and cohort stratification for STICS clinical trial

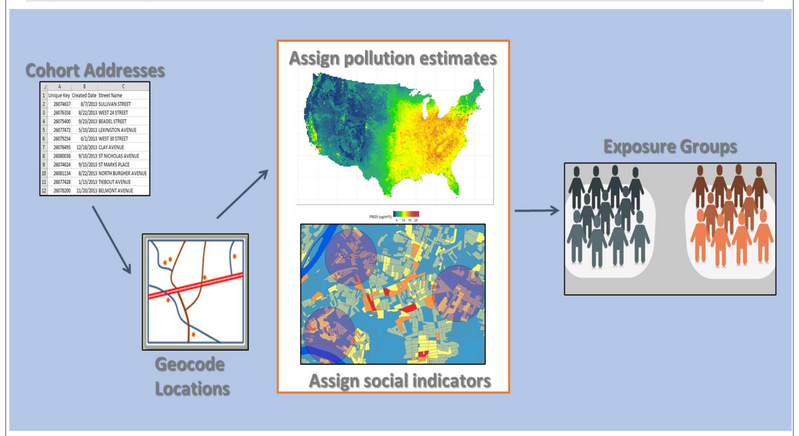


Figure 2A: Randomization scheme and treatment allocation for STICS participants

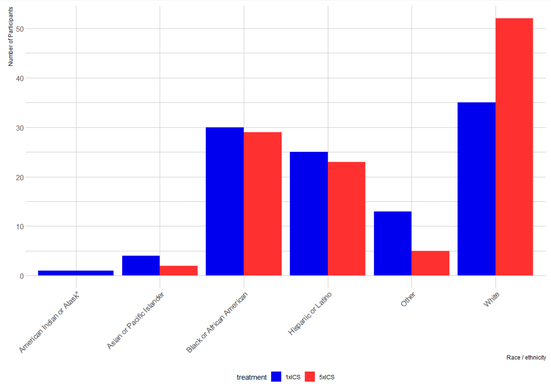
A

Run-in Phase: 4 Wk	Treatment Phase: 48 Wk		
	Randomized treatment group	Daily *except* during 7-day yellow zone	Daily *only* during 7-day yellow zone
Fluticasone 44 µg/inhalation, 2 inhalations twice daily	Low dose	Fluticasone 44 µg/inhalation, 2 inhalations twice daily	Fluticasone 44 µg/inhalation, 2 inhalations twice daily
	High dose	Fluticasone 44 µg/inhalation, 2 inhalations twice daily	Fluticasone 220 µg/inhalation, 2 inhalations twice daily

Results: Differences Between Treatment Arms

- STICS enrolled more male (64%) than female children, and more white children (39.7%) than other races.
- We found some substantial differences between treatment arms:
  - The high-dose (vs. the low-dose) arm had: a higher proportion of White children (49.6% vs 32.4%), fewer living below federal poverty line (11.0% vs 13.1%), more in MUAs (29.7% v 24.1%) (Figure 3), and a higher % with secondhand smoke exposure at home (31.5% vs 26.9%).
  - The low-dose (vs. high-dose) arm had a higher proportion of Asian or Pacific Islander children (3.7% vs. 1.8%), and children of "other" races (12.0% v 4.5%).
  - No difference in mean $PM_{2.5}$ estimates.

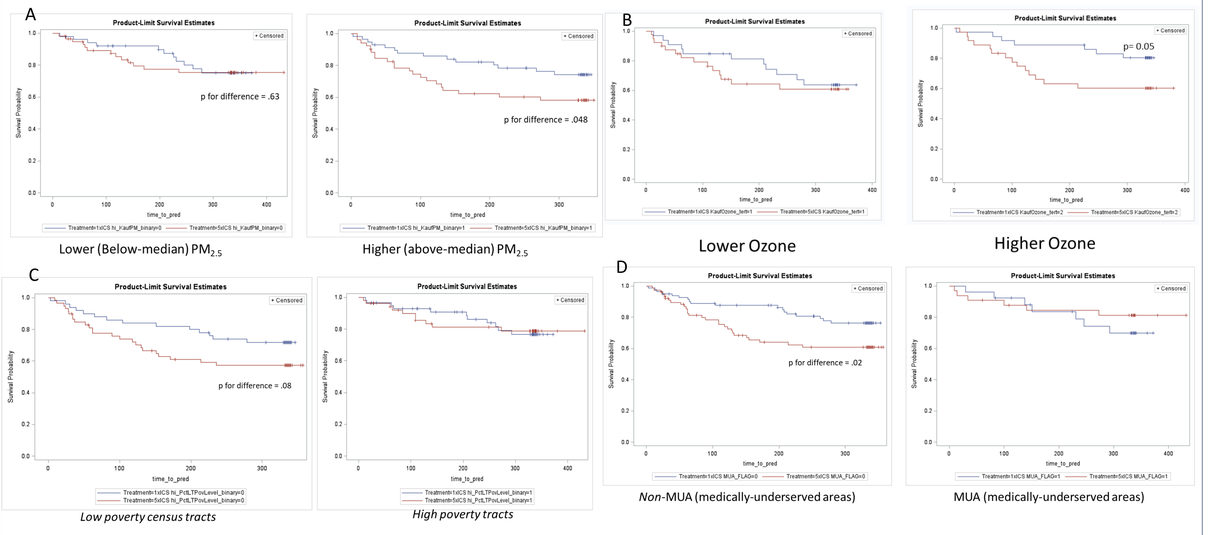
Figure 3: Participant characteristics by treatment arm.



Results: Cox Proportional Hazard Models

- High ICS dose was associated with shorter time-to-prednisone-use, compared to low ICS dose, but only among:
  - Children with above-median $PM_{2.5}$ (p = .048).
  - Living in lower-poverty areas (p = .08)
  - Living in non-MUAs (p = .02)].

Figure 4A: Time-to-prednisone use, by high ICS (red) vs. low ICS (blue) dose.



Results: Distributions

Table 1: Participant characteristics at baseline.

Characteristics	Low Rx Group (N =108)	High Rx Group (N=111)
Age at enrollment (Yrs.)	7.93 ± 2.0	8.05 ± 1.7
BMI percentile – %	66.9 ± 27.0	65.4 ± 28.5
Male sex – n (%)	67 (62.0)	74 (66.7)
Tobacco exp – n (%)	29 (26.9)	35 (31.5)
Mean $PM_{2.5}$(SD) (µg/m^3)	7.58 (1.5)	7.51 (1.5)
Mean percent below the federal poverty line (SD)	18.2 (13.1)	15.8 (11.0)
Living in MUA – n (%)	26 (24.1)	33 (29.7)
Mean O_3 (SD) – (ppm)	26.5 (4.3)	25.7 (4.4)
Mean NO_2 (SD) – (ppm)	10.7 (5.9)	10.5 (6.2)

The high-dose arm (5xICS) had a higher percentage of participants living in MUAs (29.7%) than the low-dose arm (1xICS) (24.1%).

Conclusions

- The average impact of quintupling ICS on asthma exacerbations was null in the original STICS analysis.[5]
- We found, however, that some subgroups were significantly *negatively* impacted by the higher dose:
  - Higher $PM_{2.5}$ exposures
  - Higher SEP/ less-deprived areas.
- Asthma RCTs could benefit from considering environmental and social context.

Acknowledgements

All AsthmaNet PIs, staff, participants, and committee. Funding: NIH R01HL114536-01.

References

1. Clougherty J.E., et al. The role of non-chemical stressors in mediating socioeconomic susceptibility to environmental chemicals. *Curr Environ Health Repts*. 2014
2. Rodriguez-Villamizar, L. A., "The role of socioeconomic position as an effect-modifier of the association between outdoor air pollution and children's asthma exacerbations: an equity-focused systematic review," Rev Environ Health, 2016,
3. Clougherty, J. E., et al. Geography, generalisability, and susceptibility in clinical trials. *The Lancet. Respiratory Medicine*. 2021.
4. Kirwa, K et al., "Fine-Scale Air Pollution Models for Epidemiologic Research: Insights From Approaches Developed in the Multi-ethnic Study of Atherosclerosis and Air Pollution (MESA Air)," Curr Envir Health Rpt, 2021
5. Jackson, D. J., Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. *New England Journal of Medicine*, 2018.