Modification of Treatment Efficacy in Asthma Clinical Trials by Social and Environmental Exposures

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Background

- Substantial evidence links air pollution and socioeconomic position (SEP) to asthma outcomes
- Evidence for treatment efficacy for asthma medication
 - Gold standard: Randomized Controlled Trials (RCTs)
 - Randomization balances measured and unmeasured confounders between treatment arms.

Background

- RCTs do not normally consider variations by social and environmental variables (Clougherty et al, Lancet Resp 2021)
 - Geography
 - Recruitment and retention
 - Treatment efficacy
- Few studies have investigated how these exposures may modify treatment efficacy for asthma.

AsthmaNet

 Step Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations (STICS)



STICS Cohort

- 219 children aged 5-11 yrs.
- Followed over 4-wk run-in, 48-wk treatment phase
- Randomized to two conditions:
 - Low-dose group:
 - 44 ug (2 puffs) Fluticasone 2x/day
 - High-dose group:
 - 44 ug Fluticasone (2 puffs) 2x/day
 - During exacerbation (yellow zone): 44 ug Fluticasone (10 puffs) 2x/day

STICS Cohort Primary Results



- Increasing the dose of inhaled glucocorticoids (ICS) x 5, did not reduce the number of asthma exacerbation events
- No reduction in time-to-prednisone-use

Jackson et al, A 2018

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GIS-based approach



Methods: PM_{2.5} Estimates

- PM estimates using a national universal kriging model _{(Kirwa et. al,} Early Life Env Hlth, 2021)
- Estimated for individual's Census block centroid, averaged over follow up
- Median dichotomized into high and low $\rm PM_{2.5}$ concentrations



Methods: Social Co-Exposure Indicators

Two indicators of socioeconomic position (SEP):

- Poverty Rate
 - Percent below Federal poverty level
 - ACS 5-year summary (2012-16), block group level

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 - ACS 5-year summary (2012-16), block group level
- Medically Underserved Areas (MUA)
 - Provider:population ratio
 - U.S. Health Resources and Services Administration

Methods: Statistical Analysis

- Survival analysis
 - Proc Life Test SAS
 - Confounders:
 - Race/ethnicity, household income, parental smoking, body mass index (BMI), number of household pets, city/ recruitment site, and seasonality

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- Sensitivity analyses

Cohort Description at Baseline

Table 1. Participant characteristics				
Characteristics	Total (N= 219)	Low Rx Group (N =108)	High Rx Group (N=111)	P value
Age at enrollment (Yrs.)	7.99± 1.9	7.93 ± 2.0	8.05 ± 1.7	0.64
BMI percentile – %	66.10±27.1	66.9 ± 27.0	65.4 ± 28.5	0.68
Male sex – n (%)	141 (64.3)	67 (62.0)	74 (66.7)	0.57
Primary race – n (%)				0.13
White	87 (39.7)	35 (32.4)	52 (46.9)	
Black	59 (26.9)	30 (27.7)	29 (26.1)	
Hispanic or Latino	48 (21.9)	25 (23.1)	23 (20.7)	
Asian or Pacific Islander	6 (2.74)	4 (3.70)	2 (1.80)	
American Indian/Alaskan	1(0.46)	1 (0.93)	0	
Other	18 (8.22)	13 (12.0)	5 (4.5)	
Tobacco exposure – n (%)	64 (29.2)	29 (26.9)	35 (31.5)	0.54
PM _{2.5} -(μg/m³)	7.54 (1.5)	7.58 (1.5)	7.51 (1.5)	0.74
Mean percent below federal poverty line (SD)	16.96(12.0)	18.2 (13.1)	15.8 (11.0)	0.14
Living in MUA – n (%)	59 (26.9)	26 (24.1)	33 (29.7)	0.43

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Results: PM_{2.5}

We found shorter time to prednisone use with higher ICS dose, for those with above-median $PM_{2.5}$ exposure:



Lower (Below-median) PM_{2.5}

Higher (above-median) PM_{2.5}

Results: Poverty Rate

We found shorter time-to-prednisone use with higher ICS dose, for those living in low poverty census block groups



Low poverty census tracts

Results: MUA

We found shorter time to prednisone use with higher ICS dose, for those living in non-MUA:



Non-MUA (medically-underserved areas)

MUA (medically-underserved areas)

Concluding Thoughts

- We see stronger "negative" impacts on 5xICS on Time-toprednisone in:
 - High (above-median) PM_{2.5}
 - Lower poverty areas
 - Non-MUA
 - Older children

Concluding Thoughts and Future Steps

- RCTs may benefit from consideration of social and environmental co-exposures
- Use of GIS
 - Characterization of the geographical conditions
 - Improve understanding of the lived context
 - Inform true generalizability of RCT treatment efficacy

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Questions

Thank you

Extra Slides

Results: Baseline

- Sex
- Race
- Secondhand smoke

- PM_{2.5}
- PFEV1
- Emergency visits (12 mo)

Results: Age

We found shorter time to prednisone use with higher ICS dose, for older children:



Distribution of Yellow Zone Events, by above/ below-median PM_{2.5}

Low PM_{2.5} Exposures



 Individuals with higher PM have more YZ events, on average, than do those with lower PM

Denver, CO

Percent below poverty





Saint Louis, MO

Madison, WI

