$PM_{2.5}$ and NO_2 as Potential Modifiers of Asthma Exacerbation and Control in Clinical Trials

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Background

- Substantial evidence links air pollution to asthma outcomes[1,2].
- Common clinical treatment for asthma includes inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA), although treatment response is heterogeneous[3].
- Some are nonresponsive to ICS and LABA combination, despite treatment compliance.
- Randomized clinical trials (RCTs) are the standard of evidence in medical research. Randomization balances measured and unmeasured confounders, promotes homogeneity of participant characteristics across study arms and maximizes internal validity.
- Few RCTs, however, consider whether treatment efficacy is modified by exposure to air pollution.

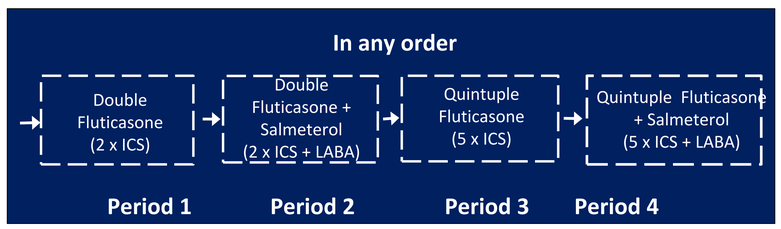
Aims

- To evaluate whether air pollutants predict asthma control days and exacerbations among a subset of the children in the BARD trial.
- To test whether exposure to ambient NO_2 and $PM_{2.5}$ alter treatment effects on asthma control days and number of exacerbations.

Methods

- Secondary analysis of AsthmaNet's Step-up Therapy in Black Children and Adults with Poorly Controlled Asthma (BARD) trial.
- Participants (n=211) were children aged 5-11 sequentially randomized to: double ICS dose (2 x ICS), double ICS with LABA (2 x ICS + LABA), quintuple ICS (5 x ICS) and quintuple ICS with LABA (5 x ICS + LABA) (**Fig 1**).
- Geocoded participant's residences, and estimated NO_2 and $PM_{2.5}$, using nationally representative universal kriging models,[4] and mixed models adjusting for age, sex, treatment, and trial site.

Figure 1: BARD RCT design. Each treatment period lasted 14 weeks (the initial two weeks of each period were considered washout periods).



Results: Asthma Control Days and Number of Exacerbations

Effects on Annualized Asthma Control

Predictors	*Estimates*	*CI*	*p*
(Intercept)	156.62	86.03 – 227.20	**<0.001**
5 x ICS	3.90	-12.40 – 20.19	0.639
5 x ICS + LABA	7.63	-8.50 – 23.76	0.353
2 x ICS + LABA	8.61	-7.61 – 24.83	0.298
Sex [M]	-29.34	-57.74 – -0.94	**0.043**
Site	-4.48	-18.49 – 9.53	0.530
Age	-0.53	-8.25 – 7.19	0.893
PM 2.5	4.12	-4.71 – 12.95	0.360

Effects on Annualized Asthma Control

Predictors	*Estimates*	*CI*	*p*
(Intercept)	157.57	86.72 – 228.42	**<0.001**
5 x ICS	4.22	-12.00 – 20.45	0.609
5 x ICS + LABA	7.52	-8.54 – 23.57	0.358
2 x ICS + LABA	8.53	-7.61 – 24.67	0.300
Sex [M]	-29.67	-58.17 – -1.18	**0.041**
Site	-2.86	-17.00 – 11.28	0.691
Age	-0.61	-8.36 – 7.14	0.877
NO2	-8.67	-17.48 – 0.13	0.054

Effects on Number of Exacerbations

Predictors	*Incidence Rate Ratios*	*CI*	*p*
2 x ICS (Ref)			
5 x ICS	0.70	0.46 – 1.09	0.114
5 x ICS + LABA	0.78	0.51 – 1.19	0.252
2 x ICS + LABA	0.55	0.34 – 0.88	**0.013**
Sex [M]	1.57	1.03 – 2.39	**0.035**
Age	0.88	0.72 – 1.07	0.211
PM 2.5	1.17	0.97 – 1.40	0.101

Effects on Number of Exacerbations

Predictors	*Incidence Rate Ratios*	*CI*	*p*
2 x ICS (Ref)			
5 x ICS	0.70	0.45 – 1.08	0.105
5 x ICS + LABA	0.76	0.50 – 1.17	0.214
2 x ICS + LABA	0.54	0.34 – 0.87	**0.012**
Sex [M]	1.53	1.00 – 2.35	**0.049**
Age	0.89	0.73 – 1.08	0.242
NO2	1.25	1.06 – 1.47	**0.010**

Table 1: Estimates (95% CI and p-values) for effects on AACD associated with treatment period and sex adjusting for recruitment site, age, $PM_{2.5}$, and NO_2. Table 2: Incidence Rate (95% CI and p-values) for the number of exacerbations associated with the treatment period, sex, age, $PM_{2.5}$, and NO_2.

Results: Exacerbations altered by PM2.5 and NO2

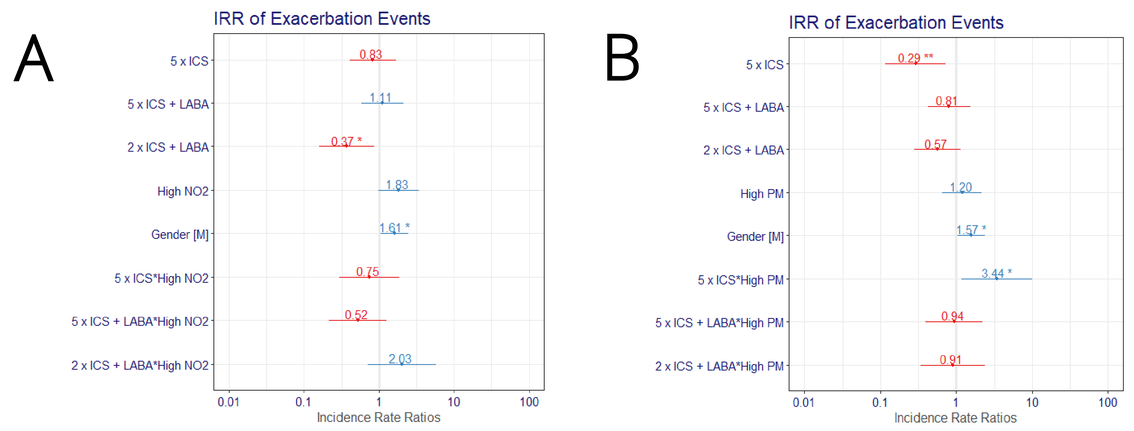


Figure 2: Forest plots of interaction between NO_2 and treatment on the number of exacerbations (Fig 2A) and $PM_{2.5}$ (Fig 2B) [Compared to 2x ICS]. Type III ANOVA = Treatment * NO_2: 6.43, p-value (0.021) and Treatment * $PM_{2.5}$: 6.48, p-value (0.017).

Implications

- Original RCT analyses showed that half the children responded better to increased ICS, and half responded better to the LABA addition, with no clear preference[5].
- We found, however, that above-average NO_2 and $PM_{2.5}$ exposure significantly negatively impacted the rate of asthma exacerbations and the number of asthma control days compared to those in the 2 x ICS group, with below median NO_2 and $PM_{2.5}$ and females.
- Ambient air pollution may alter the effects of treatment on exacerbations.

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