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

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Despite well-established associations between ambient air pollution and both asthma control and exacerbations, few RCTs have considered variation in clinical outcomes or treatment efficacy by pollutant concentrations. Richer environmental context considerations may help improve RCTs' design and interpretation.

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.

Methodology

- 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.

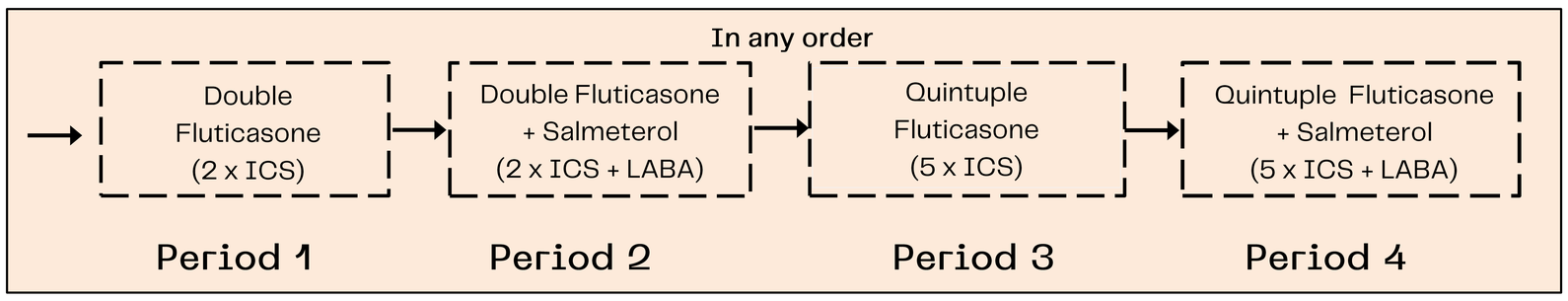

Figure 1: BARD RCT design. Each treatment period lasted 14 weeks (the initial two weeks of each period were considered washout periods).

Results: Asthma Control Days

	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

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.

Results: Asthma Exacerbations

	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 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 $PM_{2.5}$ and NO_2

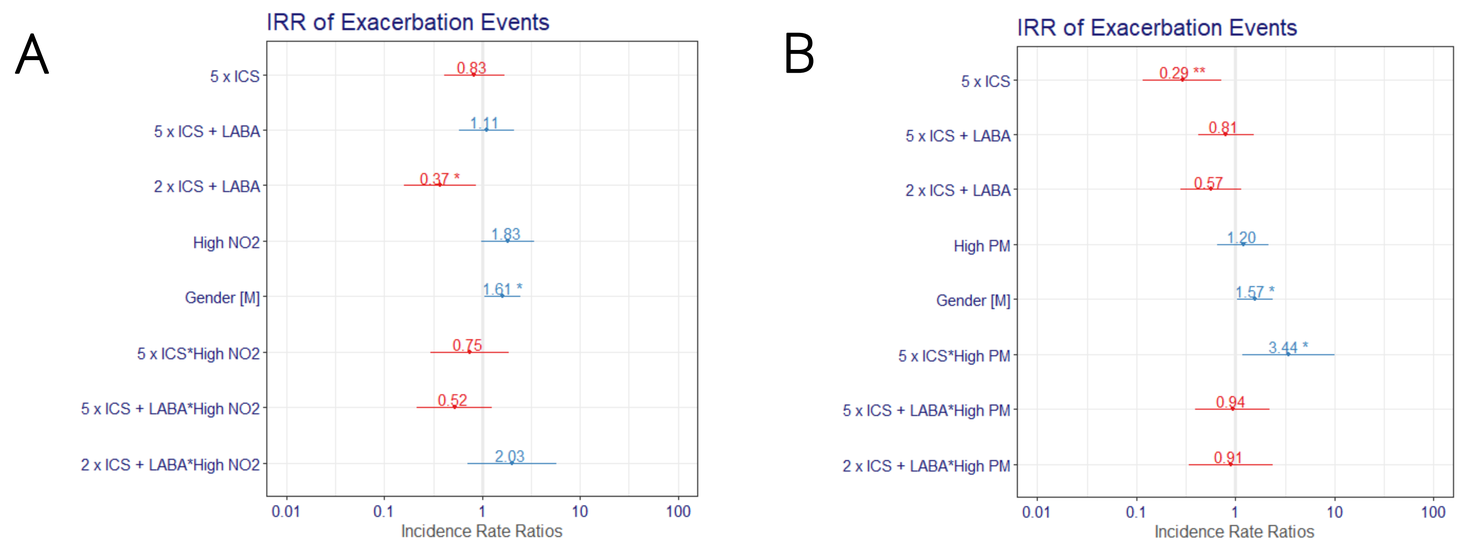

Figure 2: Forest plots of interaction between NO_2 and treatment on the number of exacerbations (Fig 2A) and $PM_{2.5}$ (Fig 2B) [**Compared to 2x ICS**]. **Type III ANOVA** = Treatment * NO_2: 6.43, p-value (0.021) and Treatment * $PM_{2.5}$: 6.48, p-value (0.017).

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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