From Gene Regulation to Metabolites: A Multi-Omics Framework for Investigating Airway Hyperresponsiveness in Pediatric Asthma

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INTRODUCTION

Airway hyper-responsiveness (AHR) is a prominent feature of asthma, with complex molecular mechanisms involving multiple pathways. This study explores how changes in miRNAs and metabolites during childhood asthma may lead to changes in AHR.

Table 1. Characteristics of the CAMP participants across three time-points with serum metabolomic profiling.

		Baseline (N = 558)		End of Trial (N = 507)		Follow-up (N = 192)	
Characteristics		**N**	**%**	**N**	**%**	**N**	**%**
Sex	**Male**	358	64.2	320	63.1	124	64.6
	Female	200	35.8	187	36.9	68	35.4
Race	**White**	393	70.4	365	72.0	136	70.8
	Black	82	14.7	71	14.0	25	13.0
	Hispanic	56	10.0	48	9.5	12	6.3
	Other	27	4.8	23	4.5	19	9.9
Treatment Group	**ICS (Budesonide)**	151	27.1	138	27.2	51	26.6
	Placebo	407	72.9	369	72.8	141	73.4
Age at blood sample	**mean (SD)[range]**	8.8(2.1)	[5.1,13.2]	12.8(2.1)	[9.1,17.2]	17.4(3)	[12.2, 25.9]
PC20 at blood sample	**mean (SD)[range]**	2.1(2.5)	[0.02, 13.3]	7.7(11.7)	[0.08,37.5]	11.6(14.9)	[0.1,37.5]

SD- Standard Deviation, PC20 - Provocative concentration of Methacholine causing a 20% reduction in lung function (Airway hyper-responsiveness Measure)

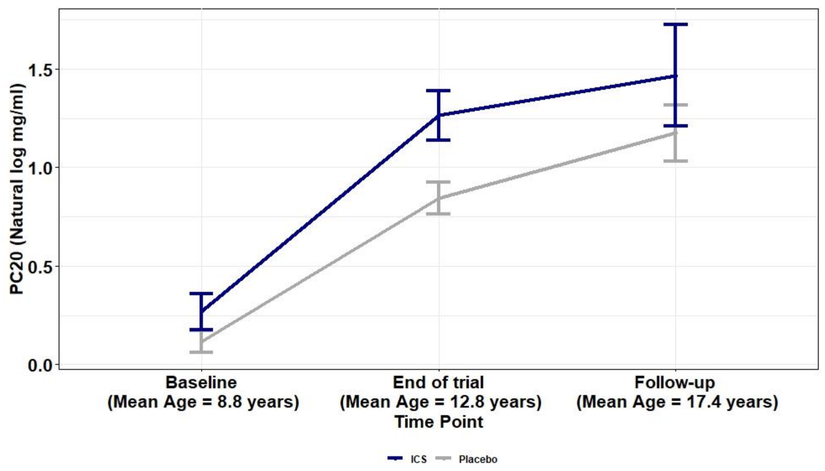

Figure 1. Mean PC20 (provocative concentration [in natural log scale] producing 20% decrease in FEV1) by treatment groups (ICS vs Placebo) and timepoint. *Error bars* are 95% confidence limits

Table 2. Association of selected asthma symptoms and clinical staff assessed asthma severity with PC20

Clinical Outcome	Estimate	RO	p-value
Asthma Severity (Moderate (versus mild) asthma)	-0.06	1.06	7.01E-07
Cough After exercise in past 6 month	-0.26	1.30	2.00E-03
Cough during day in past 6 month	-0.23	1.26	3.00E-02
Awaken from sleep in past 6 month	-0.18	1.20	3.00E-02

*RO- Relative odds of event per log decrease in PC20

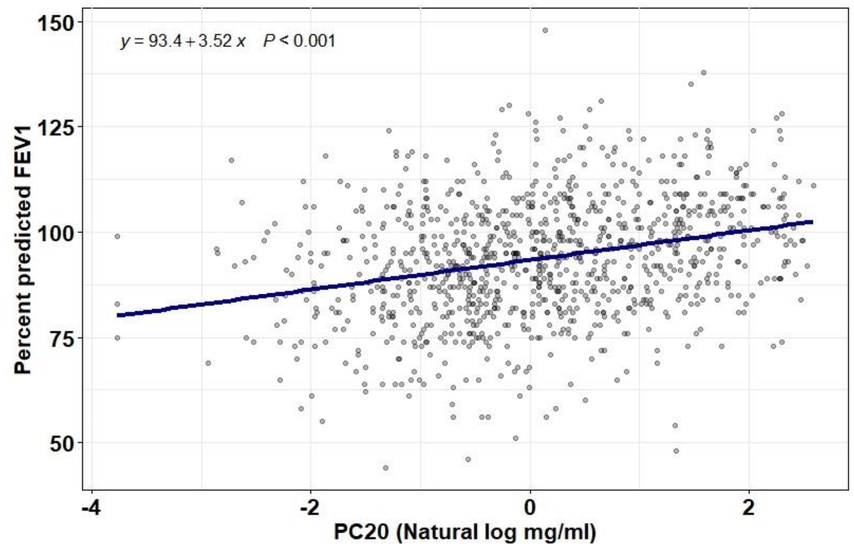

Figure 2. PC20 versus prebronchodilator FEV1 percent predicted

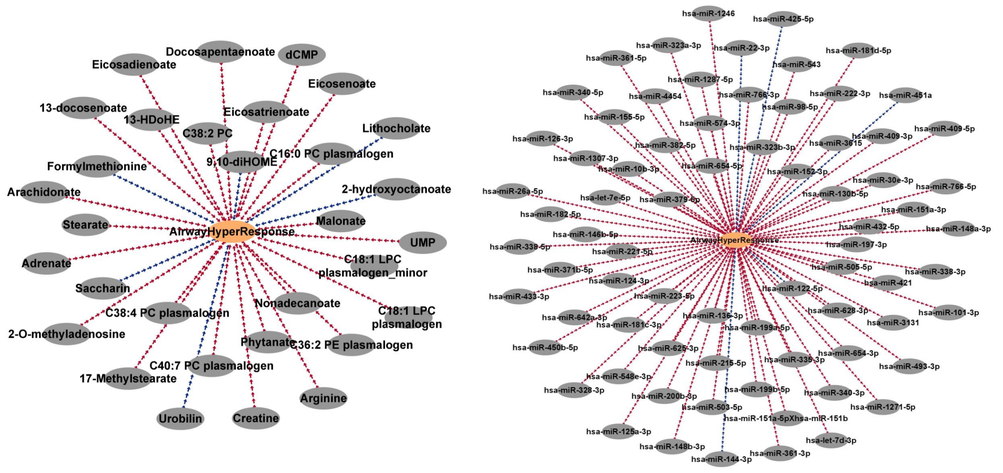

Figure 3. Metabolites and microRNAs significantly associated with airway-hyperresponsiveness (Blue: Negative association and Red: Positive association)

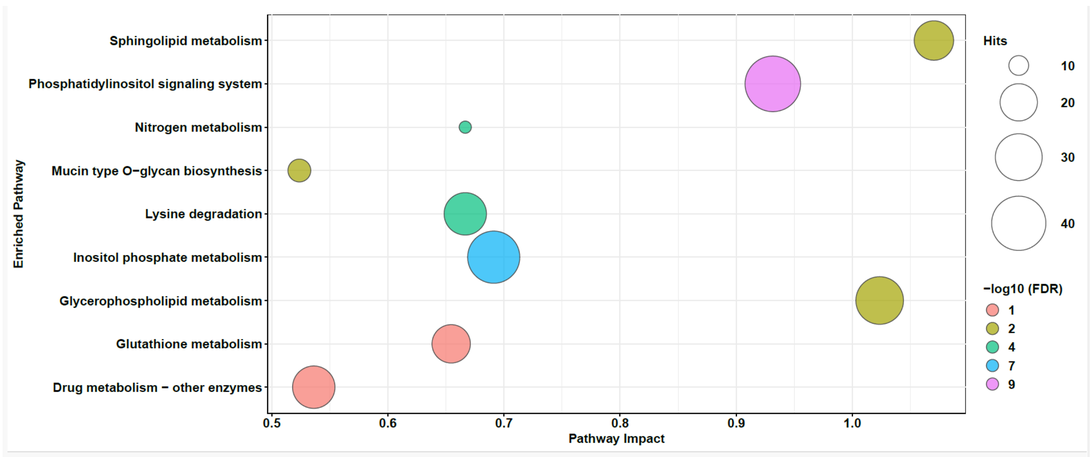

Figure 4. miRNA-targe gene and metabolite Joint Pathway Enrichment

METHODS

Childhood Asthma Management Program (CAMP) N = 1041

Lung function and PC20 was measured at time-points concurrent to (i) study baseline, (ii) end-point (~four years post-baseline) and (iii) follow-up (~ten years post-baseline) blood draws

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miRNA Sequencing
Baseline N=491
Untargeted LC-MS metabolomic profiling
Baseline N = 558
End of Trial = 507
Follow-up = 192

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- miRNA/ metabolite association with PC20 tested using linear mixed Model with adjusting model for known confounders and covariates.
- miRNA target-gene and metabolite joint pathway enrichment analysis using MetaboAnalyst version 5.

CONCLUSION

Our findings provide evidence to support broad changes in metabolites and miRNA regulation of genes accompanied general clinical trends of asthma improvement and decreasing AHR in children with mild to moderate severe asthma. These omic indicators were enriched in pathways associated with key molecular mechanisms involved in AHR. Longitudinal multiomic analysis is likely to be informative in additional populations and conditions.

ACKNOWLEDGEMENT

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