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The Association of Plasma IL-6 with Measures of Asthma Morbidity in a Moderate-Severe Pediatric Cohort Aged 6-18 Years

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Childhood asthma is a heterogenous condition with multiple endophenotypes, with most treatments focused on type 2 allergic/eosinophilic inflammation. Despite the use of treatments targeting type 2 inflammation, a subset of children continue to have asthma exacerbations. A cross-sectional analysis of adults enrolled into the National Institutes of Health/National Heart, Lung, and Blood Institute sponsored Severe Asthma Research Program-3 (SARP-3) cohort study by Peters et al. demonstrated that high plasma IL-6 is associated with metabolic dysfunction, reduced lung function, and greater asthma severity, independent of body mass index (BMI)(1). Prospective analysis of this cohort also found a strong association between plasma IL-6 and an increased rate of asthma exacerbations over a 3-year period(2). Very few studies exist evaluating peripheral blood IL-6 as a biomarker for asthma morbidity and severity in children/adolescents(3).

To determine if baseline plasma IL-6 is associated with increased asthma morbidity and severity in a pediatric cohort, data from the multicenter SARP-3 study of 155 children with asthma (median age 11.4 years, range 6.1-18.4) who completed the 3-year longitudinal study and had complete data for BMI assessment, baseline plasma IL-6 level, and asthma outcome measures were included in this analysis. The main objective of the SARP-3 study was to

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advance the understanding of severe asthma through integration of mechanistic studies with phenotype classification. SARP-3 included two baseline visits in which participants underwent detailed characterization studies and provided blood and induced sputum samples. Details of the SARP-3 protocol have previously been described(1). Plasma IL-6 was measured with a high sensitivity assay with a LLOD of 0.16pg/mL (Quantikine ELISA Kit, R&D Systems, Minneapolis, MN).

A pediatric reference interval of normal does not exist for plasma IL-6. The distribution of plasma IL-6 levels is displayed in Figure E1. The median value was 1.188 pg/mL (interquartile range, 0.803–1.806 pg/mL). Given the unknown threshold of IL-6 risk levels and the skewness of the distribution, children were stratified into quartiles according to baseline IL-6 levels: Low IL-6 (<0.805pg/mL); Med-Low IL-6 (0.805–1.19pg/mL); Med-High IL-6 (1.2–1.828pg/mL); and High IL-6 (≥1.828pg/mL). Linear, logistic, and negative binomial regression models assessed relationships between plasma IL-6 groups and BMI percentile, inflammatory markers, lung function and asthma outcomes. Longitudinal analysis evaluating the association between baseline IL-6 and asthma outcomes was performed using linear and generalized linear mixed models with a random intercept at the participant level. All analyses were adjusted for BMI and gender. IL-6 levels were significantly higher in females than males; the proportion of females was larger in the Med-High (54%) and High (42%) IL-6 groups compared to the Med-Low (26%) and Low (31%) IL-6 groups ($\chi^2_{(3)}$=7.82, p=0.049). There were no between-group differences for other potential confounders including age, race, ethnicity, household income, and ICS use (all p>0.05). Analyses were performed using STATA 16.1.

Comparable proportions of participants were Black (41%) or White (41%). Forty-three percent of the participants were healthy weight, 21% overweight, and 35% obese. On average, baseline lung function showed an obstructive pattern, with a mean FEV_1/FVC ratio of 76.7%. Ninety-five percent of participants reported using ICS over the prior 12 months. Baseline characteristics of this study population are detailed in Table E1.

Plasma IL-6 positively correlates with BMI in adults(1). Our findings were comparable in children, as increasing plasma IL-6 was associated with higher BMI percentiles (p<0.001) (Table 1). No other cross-sectional associations between IL-6 and asthma outcomes were appreciated. In contrast to what was previously reported in the adult SARP-3 cohort(1) and recent analysis of the Asthma Phenotypes in the Inner-City (APIC) pediatric cohort within the Inner-City Asthma Consortium study(3), there was no association between IL-6 and total white blood cells or blood/sputum neutrophils(Table 1). Additionally, IL-6 was not associated with type 2 inflammatory markers including blood/sputum eosinophils, serum IgE measures, or F_ENO, consistent with findings from adult and pediatric studies(1, 3)(Table 1). Higher levels of CRP were observed with increasing IL-6 levels (p<0.001)(Table 1). Elevated CRP is associated with metabolic syndrome and a predictor for diabetes(4) and cardiovascular disease. Thus, IL-6 may be a useful biomarker for the early signs of metabolic dysfunction in children with asthma, supporting a distinct asthma endotype.

The SARP-3 study design included a 3-year longitudinal follow-up period, allowing us to detect significant differences between plasma IL-6 groups, prospectively. Longitudinal

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analysis demonstrated relationships between plasma IL-6 and measures of asthma severity including propensity for asthma exacerbations requiring systemic corticosteroids and lung function impairment during follow-up. Since the low IL-6 group had markedly fewer prospective exacerbations, we combined the three medium/high IL-6 groups and found that IL-6 levels greater than or equal to 0.805pg/mL were associated with twice as many exacerbations compared to levels less than 0.805pg/mL (IRR=2.09, 95%CI [1.02, 4.28],p=0.04)(Table 2). Likewise, IL-6 levels greater than or equal to 0.805pg/mL were associated with lower FEV_1 and FVC values, β=−5.8 [−11.2,-0.5] FEV_1 and β=−6.4 [−11.6,−1.16] FVC compared to levels less than 0.805pg/mL (p=0.03 and p=0.01, respectively)(Table 2). Jackson et al. demonstrated that children with higher IL-6 had increased metabolic dysfunction and risk of asthma exacerbations during a 1-year longitudinal period; however, they found no association between IL-6 and lung function(3), potentially reflecting the longer follow-up period in this study. Our lung function findings are consistent with the adult SARP-3 cohort results, and provides new evidence that children with higher plasma IL-6 levels have worse lung function, risk of exacerbation, and increased severity, adjusting for BMI.

The mechanism through which peripheral blood IL-6 plays a role in asthma pathogenesis is largely unknown, although multiple processes have been suggested(5). Recent data suggest IL-6 is directly linked to airway inflammation (6–8). IL-6 blockade may be a potential target for asthma treatment; tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, was an effective treatment in two pediatric patients with severe persistent asthma(9).

Strengths of our study include a well-phenotyped cohort of children with severe asthma, analysis of plasma IL-6 with identical assay used in the adult SARP-3 cohort allowing for direct comparisons with adult data, and a 3-year prospective follow-up period. Limitations include a modest sample size, lack of control cohort without asthma, and a longer recall from baseline potentially explaining the lack of cross-sectional findings. We did not find a statistically significant association between plasma IL-6 and total WBC and blood neutrophil levels as was demonstrated in the APIC pediatric cohort(3). One plausible reason may be that the cohorts are phenotypically different at baseline. In contrast to the APIC cohort, the SARP-3 pediatric cohort was enriched with children having severe asthma and higher baseline levels of total serum IgE, FeNO, and blood eosinophil, suggesting a more skewed Th2 population. Nonetheless, higher IL-6 quartiles trended towards elevated total WBC and blood neutrophil levels, and perhaps a larger sample size would have provided greater statistical power needed to demonstrate significant associations.

In conclusion, higher plasma IL-6 levels in children are significantly associated with elevated BMI, early signs of metabolic dysfunction evidenced by high CRP, and greater asthma severity with risk for both asthma exacerbation and lower lung function based on longitudinal analyses. This is consistent with previous work in adults with asthma and the first to show lower lung function in children with high IL-6 levels. Further mechanistic and therapeutic IL-6 studies are needed to determine the clinical relevance of these findings.

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Extended Data

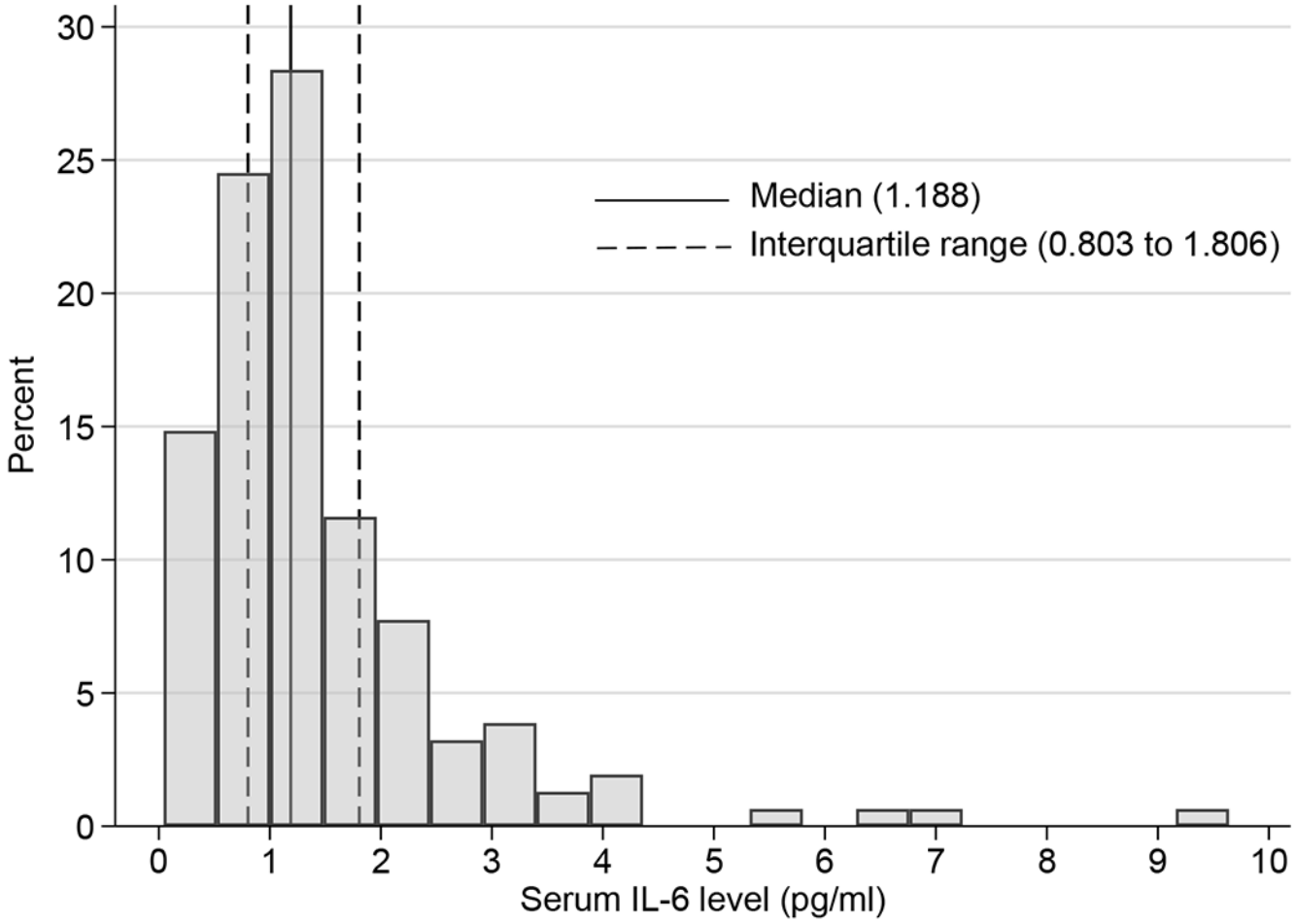

Fig E1.
Distribution of plasma IL-6 level (N=155) with 25th and 75th percentiles (dashed lines); 0.16 pg/mL is the lower limit of detection.

TABLE E1.

Baseline Characteristics of Study Population (n = 155)

Characteristic	No. (%)
Demographics	
Age (yrs), median (range)	11.4 (6.1-18.4)
Male gender	96 (62)
Race	
American Indian/Alaska Native	1 (1)
Asian	0 (0)
Black/African American	63 (41)
Mixed race	26 (17)

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Characteristic	No. (%)
Native Hawaiian/Other Pacific Islander	1 (1)
White	64 (41)
Hispanic ethnicity	22 (14)
Annual household income <$25,000	51 (37)
Clinical characteristics	
BMI category	
Underweight (<5th percentile)	2 (1)
Normal weight (5th - <85th percentile)	66 (43)
Overweight (85th - <95th percentile)	33 (21)
Obese (≥95th percentile)	54 (35)
ACT score, mean (SD)[1]	18.2 (4.5)
≥ 1 asthma exacerbation in past year	101 (66)
ICS use over prior 12 months	147 (95)
Severe Asthma[*]	89 (57)
Blood markers of atopy/inflammation	
≥ 1 positive specific IgE[3]	138 (91)
Serum IgE conc (kU/L), mean (SD)[4]	868 (1328)
Blood eosinophil count (cells/uL), mean (SD)[5]	395 (296)
F_ENO (ppb), mean (SD)[2]	35.7 (37.8)
Pulmonary function testing[6]	
FEV_1 % predicted, pre-bronchodilator, mean (SD)	90.5 (14.1)
FVC % predicted, pre-bronchodilator, mean (SD)	103.5 (13.0)
FEV_1/FVC, pre-bronchodilator, mean (SD)	76.7 (8.8)
FEV_1 % predicted max. absolute reversibility, mean (SD)	12.3 (12.5)

[1] n = **155** ACT scores

[2] n = **152** F_ENO samples

[3] n = **152** specific IgE samples

[4] n = **146** IgE samples

[5] n = **155** CBC samples

[6] n = **155** PFTs

[*] The classification of severe asthma was determined using criteria from the American Thoracic Society/European Thoracic Society guidelines.

Abbreviations: BMI = body mass index; ACT = Asthma Control Test; ICS = inhaled corticosteroid; IgE = immunoglobulin E; F_ENO = fraction of exhaled nitric oxide; ppb = parts per billion; SD = standard deviation; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second

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REFERENCES

1. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. Lancet Respir Med. 2016;4(7):574–84. [PubMed: 27283230]
2. Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet Jc, et al. Evidence for Exacerbation-Prone Asthma and Predictive Biomarkers of Exacerbation Frequency. Am J Respir Crit Care Med. 2020.
3. Jackson DJ, Bacharier LB, Calatroni A, Gill MA, Hu J, Liu AH, et al. Serum IL-6: A biomarker in childhood asthma? J Allergy Clin Immunol. 2020.
4. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001;286(3):327–34. [PubMed: 11466099]
5. Rincon M, Irvin CG. Role of IL-6 in asthma and other inflammatory pulmonary diseases. Int J Biol Sci. 2012;8(9):1281–90. [PubMed: 23136556]
6. Jevnikar Z, Östling J, Ax E, Calvén J, Thörn K, Israelsson E, et al. Epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation. J Allergy Clin Immunol. 2019;143(2):577–90. [PubMed: 29902480]
7. Massoud AH, Charbonnier LM, Lopez D, Pellegrini M, Phipatanakul W, Chatila TA. An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to TH17-like cells. Nat Med. 2016;22(9):1013–22. [PubMed: 27479084]
8. Harb H, Stephen-Victor E, Crestani E, Benamar M, Massoud A, Cui Y, et al. A regulatory T cell Notch4-GDF15 axis licenses tissue inflammation in asthma. Nat Immunol. 2020.
9. Esty B, Harb H, Bartnikas LM, Charbonnier LM, Massoud AH, Leon-Astudillo C, et al. Treatment of severe persistent asthma with IL-6 receptor blockade. J Allergy Clin Immunol Pract. 2019;7(5):1639–42 e4. [PubMed: 30885880]

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Clinical Implications:

Higher plasma IL-6 levels in children are significantly associated with elevated body mass index, early signs of metabolic dysfunction evidenced by high CRP, and greater asthma severity with risk for both asthma exacerbation and lower lung function.

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TABLE 1.

Associations between Plasma IL-6, Asthma Outcome Measures, and Baseline Markers of Inflammation

Cross-sectional*	Low IL-6 (n=39)	Med-Low IL-6 (n= 39)	Med-High IL-6 (n= 39)	High IL-6 (n= 38)	p-value**
Clinical Outcome Measures					
BMI Percentile, mean (SD)	63.2 ± 27.4	79.3 ± 20.8[a]	84.8 ± 19.3[a]	78.1 ± 30.8[a]	**<0.001**
Asthma exacerbation in the past yr, mean (SD)***	1.1 ± 1.2	2.1±2.8	2.5±3.3	1.8±1.9	0.13
Health care utilization for asthma in the past yr, n (%)	23 (59)	24 (62)	23 (59)	24 (63)	0.98
ER visit for asthma in the past yr, n (%)	16 (41)	22 (56)	23 (59)	18 (47)	0.72
Hospitalization for asthma in the past yr, n (%)	9 (23)	12 (31)	7 (18)	11 (29)	0.40
Missed days of school in the past yr, mean (SD)	3.8 ± 8.6	2.8 ± 6.6	4.8 ± 14.7	2.0 ± 4.1	0.64
Severe asthma, n (%)[§]	20 (51)	25 (64)	21 (54)	23 (61)	0.54
Spirometry Outcome Measures					
FEV_1 (% predicted), mean (SD)	93.8 ± 11.4	89.8 ± 13.6	90.2 ± 16.1	88.1 ± 15.0	0.22
FVC (% predicted), mean (SD)	105.5 ± 9.9	102.3 ± 15.1	104.0 ± 10.5	102.2 ± 15.9	0.21
FEV_1/FVC, mean (SD)	77.8 ± 7.3	77.0 ± 9.2	75.7 ± 9.5	76.1 ± 9.3	0.85
FEV_1 (% predicted) max. absolute reversibility, mean (SD)	10.8 ± 11.5	11.2 ± 9.5	15.6 ± 15.8	11.7 ± 12.3	0.50
Non-Th2 Biomarkers					
Plasma CRP log_{10}, mean (SD)	10.9 ± 1.3	11.7 ± 1.3	12.4 ± 1.1[b]	12.9 ± 1.5[b]	**<0.001**
Total white blood cells (K/uL), mean (SD)	6.3 ± 2.2	6.8 ± 2.8	7.1 ± 1.9	7.5 ± 2.0	0.71
Blood neutrophils (cells/uL), mean (SD)	2933 ± 2068	3332 ± 2467	3587 ± 1673	3945 ± 1713	0.71
Sputum neutrophils (%), mean (SD)	35.4 ± 17.7	49.4 ± 25.9	42.2 ± 24.2	58.6 ± 21.7	0.27
Th2 Biomarkers					
Blood eosinophils (cells/uL), mean (SD)	472 ± 332	362 ± 268	362 ± 290	383 ± 285	0.45
Sputum eosinophils (%), mean (SD)	17.2 ± 25.4	5.2 ± 7.8	5.7 ± 15.2	3.3 ± 5.0	0.54
Serum IgE Measures					
IgE (kU/L), mean (SD)	916 ± 1186	740 ± 1356	867 ± 1614	938 ± 1141	0.96
≥ 1 positive specific IgE, n (%)	36 (92)	32 (84)	36 (95)	34 (92)	0.43
F_ENO (ppb), mean (SD)	40.2 ± 37.8	35.5 ± 25.1	35.7 ± 41.9	31.2 ± 44.5	0.84

[a]=p<0.01 vs. Low IL-6;

[b]= p<0.001 vs. Low IL-6

*There was full data for all outcomes (n=155) with exception of 40 sputum samples, 146 IgE samples, 152 specific IgE, and 152 F_ENO samples

**The p values were generated from linear, logistic, and negative binomial regression models, adjusted for BMI status (healthy weight, overweight, obese) and gender.

***Asthma exacerbation was defined as a burst of systemic corticosteroid lasting ≥ 3 days for treatment of worsening asthma control.

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[§]The classification of severe asthma was determined using criteria from the American Thoracic Society/European Thoracic Society guidelines.

Abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; FEF_{25-75} = forced expiratory flow between the 25^{th} and 75^{th} percentile of forced vital capacity; SD = standard deviation; CRP = C-reactive protein; IgE = Immunoglobulin E; F_ENO = fraction of exhaled nitric oxide; ppb = parts per billion

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TABLE 2.

Associations between Plasma IL-6 and Asthma Outcome Measures During 3-Year Longitudinal Follow-Up (three 1-year measurements after baseline, n=8 subjects missing follow-up data)

Longitudinal	Low IL-6 (n=37)	Med-High IL-6[§] (n=110)	Effect size (95% CI)	p-value[*]
Clinical Outcome Measures				
Asthma exacerbation rate per yr, mean (SD)[**]	0.40 (0.87)	0.97 (1.90)	IRR = 2.09 (1.02, 4.28)	**0.04**
One-year follow-up	0.33 (0.79)	1.19 (2.40)		
Two-year follow-up	0.53 (1.11)	0.91 (1.64)		
Three-year follow-up	0.33 (0.66)	0.75 (1.33)		
Proportion of participants with ER visit for asthma per yr, % (n)	12 (12)	27 (79)	OR = 3.41 (0.88, 13.1)	0.08
One-year follow-up	17 (6)	33 (36)		
Two-year follow-up	12 (4)	26 (26)		
Three-year follow-up	7 (2)	21 (17)		
Spirometry Outcome Measures				
FEV_1 (% predicted), mean (SD)	93.1 (9.6)	88.3 (16.2)	β = −5.8 (−11.2, −0.5)	**0.03**
One-year follow-up	93.2 (10.2)	88.6 (15.5)		
Two-year follow-up	95.1 (9.6)	87.4 (16.8)		
Three-year follow-up	91.0 (8.9)	88.9 (16.5)		
FVC (% predicted), mean (SD)	104.8 (11.3)	101.4 (15.2)	β = −6.4 (−11.6, −1.16)	**0.01**
One-year follow-up	105.0 (11.2)	101.3 (14.3)		
Two-year follow-up	105.2 (11.4)	101.1 (15.3)		
Three-year follow-up	104.0 (11.5)	101.9 (16.2)		

[§] IL-6 levels greater than or equal to 0.805pg/mL

[*] The p values were generated from mixed effects linear, logistic, and negative binomial regression models, adjusted for year, BMI status (healthy weight, overweight, obese), gender, and participant random intercept.

[**] Asthma exacerbation was defined as a burst of systemic corticosteroid lasting ≥ 3 days for treatment of worsening asthma control.

Abbreviations: FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; IRR=incidence rate ratio; OR = odds ratio; β = beta; CI = confidence interval; SD = standard deviation