Received: 2 November 2017 | Accepted: 16 February 2018
DOI: 10.1002/ppul.23983

ORIGINAL ARTICLE: ASTHMA

WILEY PEDIATRIC PULMONOLOGY

Divergent transcriptional profiles in pediatric asthma patients of low and high socioeconomic status

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Funding information
National Institutes of Health, Grant numbers: HL108723, HL122328

Abstract

Aim: There are marked socioeconomic disparities in pediatric asthma control, but the molecular origins of these disparities are not well understood. To fill this gap, we performed genome-wide expression profiling of monocytes and T-helper cells from pediatric asthma patients of lower and higher socioeconomic status (SES).

Method: Ninety-nine children with asthma participated in a cross-sectional assessment. Out of which 87% were atopic, and most had disease of mild (54%) or moderate (29%) severity. Children were from lower-SES (n = 49; household income <$50 000) or higher-SES ($n$ = 50; household income >$140 000) families. Peripheral blood monocytes and T-helper cells were isolated for genome-wide expression profiling of mRNA.

Results: Lower-SES children had worse asthma quality of life relative to higher-SES children, by both their own and their parents' reports. Although the groups had similar disease severity and potential confounds were controlled, their transcriptional profiles differed notably. The monocytes of lower-SES children showed transcriptional indications of up-regulated anti-microbial and pro-inflammatory activity. The T-helper cells of lower-SES children also had comparatively reduced expression of genes encoding γ-interferon and tumor necrosis factor-α, cytokines that orchestrate Type 1 responses. They also showed up-regulated activity of transcription factors that polarize cells towards Type 2 responses and promote Th17 cell maturation.

Conclusion: Collectively, these patterns implicate pro-inflammatory monocytes and Type 2 cytokine activity as mechanisms contributing to worse asthma control among lower-SES children.

KEYWORDS
asthma, cytokines, health disparities, pediatrics

1 | INTRODUCTION

There is appreciable variability in the clinical outcomes of children with asthma. Multiple factors contribute to this variability, including genetics, disease phenotype, care quality, trigger control, and medication adherence.[1] Above and beyond these factors, children's outcomes also pattern by their family's socioeconomic status (SES). Compared with their more advantaged peers, lower-SES children with asthma have worse disease control, more school absences, more functional limitations, more hospital admissions, and higher mortality.[2–5]

The pathologic basis of these disparities is starting to be understood, particularly in atopic patients whose disease is

eosinophilic.[6,7] Relative to their advantaged peers, lower-SES children display more pronounced Type 2 cytokine[8,9] and airway inflammatory[10] responses to asthma triggers. They also show indications of a sustained late-phase response, as reflected in higher circulating eosinophil counts[9] and greater alveolar nitric oxide content.[11] Nevertheless, the molecular underpinnings of this dysregulation remain poorly understood. Here we sought to fill this gap by conducting genome-wide expression profiling on two populations of cells with roles in asthma control: CD14+ monocytes and CD3+/CD4+ T-helper lymphocytes.

Upon inhaled allergen exposure, monocytes are recruited from the blood into the lungs, where they can mature into dendritic cells and airway macrophages.[12] Along with airway epithelia, these cells function as sentinels,[13] which detect allergens, irritants, and pathogens, and steer T-helper lymphocytes to differentiate into distinct functional phenotypes. Based on studies of healthy individuals,[14,15] we predicted the monocytes of low-SES children would display indications of up-regulated activity, especially in transcriptional pathways that orchestrate antimicrobial and inflammatory responses, like those mediated by AP-1, GATA, NF-κB, and ELK-1.

T-helper lymphocytes are key drivers of the airway pathology that initiates and maintains asthma. Distinct functional phenotypes of these cells propagate effector functions that contribute to allergic sensitization, eosinophil and neutrophil recruitment, as well as downstream inflammation, remodeling, and hypersensitivity of the airways.[16] Based on studies of cytokine production and airway inflammation,[8,9,11,15,17,18] we hypothesized that lower-SES children would display transcriptional profiles indicative of up-regulated T-helper lymphocyte activity with a polarization away from Type 1 cytokine profiles and toward Type 2 and/or Type 17 profiles. We reasoned this would be evident in transcripts and networks that coordinate antigen recognition and cellular differentiation, and mobilize Types 1 and 2 effector functions.

2 | MATERIALS AND METHODS

2.1 | Patients

This cross-sectional analysis focuses on 99 children with asthma from either lower-SES ($n = 49$) or higher-SES ($n = 50$) families. They were drawn for a gene-expression sub-study from a larger cohort of 308 patients[19] and represent the poles of that sample's SES distribution. Patients in the larger cohort were recruited between July 2013 and July 2016 from one health care system, NorthShore University HealthSystem, and one federally qualified health center, Erie Family Health Center, both in Evanston, Illinois. Children in the higher-SES group were in the upper 15% of the larger sample's income distribution. All had family incomes exceeding $140 000 per year, and none was receiving government assistance. Children in the lower-SES group were in the bottom 15% of the larger sample's income distribution. All had family incomes below <$50 000 per year and/or received government assistance. For the larger project, we screened a total of 494 children, 452 of whom were eligible for participation. Inclusion criteria were (a) ages 8-17, (b) fluency in English, and (c) physician diagnosis of asthma. Exclusion criteria were other chronic medical or psychiatric illness, and acute respiratory illness within 2 weeks. Of the 452 eligible children, 144 ultimately did not participate, because they either declined to do so following screening ($n = 48$), revoked consent ($n = 3$), or never attended an assessment ($n = 93$). The protocol was approved by the Institutional Review Boards of Northwestern University, NorthShore University HealthSystem, and Erie Family Health Center. All children gave written assent before participating, and a caregiver provided written consent.

2.2 | Socioeconomic status

Each child's caregiver was interviewed using items from the MacArthur Sociodemographic Questionnaire, which provides detailed information regarding family income, education, and resources.

2.3 | Isolation of cells and extraction of RNA

Twenty millilitre of antecubital blood was drawn into Cell Preparation Tubes (Becton-Dickinson, Franklin Lakes, NJ). Following the manufacturer's protocol, peripheral blood mononuclear cells (PBMC) were isolated by density-gradient centrifugation. After washing, PBMC were incubated for 15 min at +4°C with immuno-magnetic beads (Miltenyi Biotec, Auburn, CA), then washed again. The re-suspended cells were passed through an automated cell sorter (autoMACS Pro; Miltenyi Biotec), whose magnetic columns enabled positive selection of monocytes (CD14+) and T-helper lymphocytes (CD3+/CD4+), with >90% purity as verified by flow cytometry. The isolated cell populations were then disrupted and homogenized by centrifugation in Qiashredder tubes containing RLT Plus Buffer (Qiagen, Frederick, MD). The resulting lysates were frozen at −80°C until the study ended. At that point, total RNA was extracted using PCR-clean and RNAse-free techniques with a commercially available kit (Qiagen RNeasy).

2.4 | Gene expression profiling

Before analysis, RNA was tested for suitable mass (median = 491.49 ng) and integrity (median RIN = 8.5) on NanoDrop 1000 (Thermo Fisher Scientific, Waltham, MA) and Agilent TapeStation instruments (Agilent Technologies, Santa Clara, CA). All but three samples (in each case, from CD14+ monocytes) passed a standard endpoint quality criterion (median probe fluorescence intensity >100). The three failing samples (One Lower-SES, Two higher-SES) were dropped from the CD14+ data set. Fluorescently-labeled cRNA targets were synthesized using a commercially available kit (Ambion TotalPrep), and hybridized to Illumina HT-12 v4 bead arrays, which were read on an Illumina iScan Station (San Diego, CA) at the UCLA Neuroscience Genomics Core. This array covers more than 34 000 transcripts, including the vast majority of named human genes, and we have used it extensively in past research.[14,20] Raw data are deposited in the Gene Expression Omnibus repository (Accession # GSE109455).

2.5 | Asthma quality of life

Each child completed the Pediatric Asthma Quality of Life Questionnaire.[21] This 23-item measure produces an overall score, as well as

subscales that assess emotional difficulties, symptom burden, and activity limitations. These scales have been extensively validated, and showed high internal consistency her (Cronbach's alphas >0.85). To obtain collateral information, we also asked caregivers to complete the same questionnaire with respect to their child's status. In each domain, higher scores indicate better quality of life.

2.6 | Covariates

A priori, we identified a panel of covariates which might give rise to spurious associations between children's SES and gene expression profiles. They included age, gender, racial group (coded as Caucasian/Non-Hispanic vs Other), body mass index (BMI), asthma severity, and medication use. BMI was calculated as kg/m^2 based on measurements taken with a balance-beam scale and stadiometer. Disease severity was coded based on guidelines from the National Asthma Education and Prevention Program/Expert Panel Report 2, and reflects the higher of medication use and symptom frequency.[22] Children also brought their medications to the assessment and reported how many days in the past week they had used each; we coded these agents into categories reflecting short-acting β-agonists (SABA) and inhaled corticosteroids (ICS).

2.7 | Statistical analyses

Aside from the three patients with unsatisfactory CD14+ RNA, the dataset was complete and without missing values. Using higher-order bioinformatic analyses, we sought to identify socioeconomic differences in the activity of transcription control pathways and functional genomic categories. Accordingly, our results emphasize findings from these higher-order analyses, and intentionally downplay results for individual transcripts. Briefly, we estimated transcript abundance using default algorithms in Illumina GenomeStudio. After the raw data were quantile-normalized and log2-transformed, linear models were used to quantify the magnitude of differential gene expression between lower-SES and higher-SES groups, while adjusting for covariates. The pool of transcripts showing >1.20-fold differential expression between groups served as input into higher-order bioinformatic analyses, which maintain their own false discovery rates. Defining differential gene expression by point estimates of biological magnitude (ie, fold thresholds) yields more replicable higher-order findings than does screening input based on *P*-/*q*-values.[23,24] First, to identify common functional characteristics of differentially expressed genes, we conducted Gene Ontology analyses using GOstat (http://gostat.wehi.edu.au). This statistical tool identifies sets of functional related transcripts using Benjamin-corrected *P*-values to protect against false discoveries. Second, we used the Transcription Element Listening System (TELIS; http://www.telis.ucla.edu) to identify upstream transcription control pathways contributing to patterns of differential gene expression. TELiS identifies these pathways based on asymmetries in the prevalence of transcription factor-binding motifs in the promoters of differentially expressed genes.[25] Standard errors for bioinformatic results were derived from bootstrap resampling of residual vectors from the linear models, which controls for the inter-correlation amongst transcripts.

3 | RESULTS

Table 1 describes the sample. As explained in Methods, the patients were selected from a larger cohort to be from the lower or higher ends of the SES distribution, and accordingly the groups differed markedly on family income and government assistance. The bulk of children in the lower-SES group identified as racial or ethnic minorities, whereas most of those in the higher-SES group did not (65% vs 6% as African-Americans). On average, the lower-SES children had higher body mass index than the higher-SES children (means of 24.9 vs 21.0), and reported marginally less frequent SABA use (2.4 vs 1.5 days in past week). The groups were similar with regard to age, gender, atopy, ICS use, and asthma severity. Nevertheless, to minimize confounding, all these variables were included as covariates in transcriptional analyses below.

3.1 | Quality of life

Mirroring the broader literature, lower-SES children had worse asthma-related quality of life compared with higher-SES children (see Figure 1). On caregiver reports, these SES disparities were apparent for the scale's total score, and subscales reflecting activity limitations, emotional functioning, and symptom burden (all *P*-values <0.001). Children's reports showed the same pattern, with significant SES disparities on all dimensions (*P*-values <0.02) except symptom burden, where the difference was marginal ($P = 0.08$).

3.2 | CD14+ gene expression

Linear-model analyses with control for covariates identified 49 monocyte transcripts showing a ≥1.20-fold difference in expression according to SES (Table 2). Thirty-three of these transcripts showed a relative up-regulation among lower-SES children. Gene Ontology categories that were over-represented among these transcripts included chemokine activity (GO: 0008009; $P = 0.0003$; three hits including *CCL2*, *CCL4L1*, *LOC728830*) and wound healing (GO:0009611; $P = 0.008$; four hits including *CCL2*, *LOC728830*, *CD9I*, *PROK2*). Lower-SES children also showed relative up-regulation of genes encoding components of the MHC Class 2 complex (eg, *HLADRB1*, *HLADRB5*, *HLADRB6*) and proteins involved in antigen processing and presentation (eg, *CD9*, *CTSG*, *ERAP2*). Consistent with these patterns, and with our hypotheses, TELIS analyses of transcription control pathways indicated relatively increased activity of AP-1 (TRANSFAC V$AP1_Q2 motif; fold difference = 2.13, SE = 0.81, $P = 0.018$) and ELK-1 (TRANSFAC V$ELK1_01 motif; fold difference = 2.01, SE = 0.78, $P = 0.035$) in monocytes of lower-SES children (Figure 2, upper panel). These transcription factors coordinate gene expression programs that foster maturation, mobilization, and activation of monocytes.

TABLE 1 Characteristics of the analytic sample ($N = 99$)

	Lower-SES group ($N = 49$) mean (SD) or N (%)	Higher-SES group ($N = 50$) mean (SD) or N (%)	Group difference (P-value)
Annual family income, dollars	37 053 (17 070)	260 187 (321 789)	0.0001
Family receives federal assistance	35 (74.1%)	0 (0.0%)	0.0001
Child age, years	12.7 (2.9)	13.0 (2.5)	0.57
Child sex, female	22 (44.9%)	22 (44.0%)	0.55
Child identifies as White race	8 (16.3%)	35 (70.0%)	0.0001
Child identifies as Black race	32 (65.3%)	3 (6.0%)	0.0001
Child identifies as Hispanic ethnicity	10 (20.4)	6 (12.0)	0.19
Child body mass index (kg/m^2)	24.9 (6.6)	21.0 (4.4)	0.001
Atopy, positive	40 (81.6%)	43 (86.0%)	0.60
Days child used ICS, past week	2.7 (2.9)	3.3 (3.3)	0.34
Days child used SABA, past week	2.4 (2.5)	1.5 (2.0)	0.05
Child's asthma severity category			0.37
Mild intermittent	8 (16.3%)	7 (14.0%)	
Mild persistent	14 (28.6%)	24 (48.0%)	
Moderate	18 (36.7%)	11 (22.0%)	
Severe	9 (18.4%)	8 (16.0%)	

Among the 16 transcripts down-regulated in monocytes of lower-SES children were heat-shock and cell-stress proteins (*HSPA1A*, *HSPA1B*, *DNAJB1*). Consistent with this pattern, TELIS analyses indicated down-regulated activity of the HSF-1 (TRANSFAC V$HSF1_01 motif; fold difference = 0.34, SE = 0.11, $P = 0.0001$) and HSF-2 (TRANSFAC V$HSF2_01 motif; fold difference = 0.40, SE = 0.14, $P = 0.003$) transcription control pathways in lower-SES children (Figure 2, upper panel). These pathways mediate heat-shock protein signaling.

3.3 | CD3+/CD4+ gene expression

Covariate-adjusted linear-models identified 73 transcripts in T-helper lymphocytes showing a >1.20-fold difference in expression by SES (Table 3). Thirty-nine of those transcripts were relatively down-regulated among lower-SES children. The Gene Ontology categories over-represented among these transcripts included anti-viral response, as reflected in down-regulated expression of the canonical Type 1 cytokines γ-interferon and tumor necrosis factor-α (GO:0009615; two hits, $P = 0.015$), which orchestrate Type 1 immune responses against intracellular pathogens. Also over-represented among down-regulated transcripts were categories reflecting cellular differentiation and cellular development (GO:0030154 and GO:030154; both p's = $p = 0.0003$; both categories with nine hits including *PMAIP1*, *HSPA1A*, *RHOB*, *IER3*, *GADD45G*, *IFNG*, *TNF*, *SPATA20*). Thirty-four T-helper cell transcripts were relatively up-regulated in lower-SES children, including a number whose expression is indicative of cellular activation (*HLADRB1*, *HLADRB5*, *HLADRB6*, *FCGBP*).

Consistent with these patterns, TELiS analyses found T-helper lymphocytes of lower-SES children to display relative up-regulated activity of the AP-1 (TRANSFAC V$AP1_Q2 motif; fold difference = 1.83, SE = 0.59, $P = 0.030$) and GATA (TRANSFAC V$GATA_C motif; fold difference = 2.18, SE = 0.76, $P = 0.019$) (Figure 2, lower panel) transcriptional pathways. These pathways are involved in T-lymphocyte proliferation and differentiation, and GATA-3 in particular is involved in mobilizing Type 2 effector functions. TELIS further indicated that lower-SES children had relatively up-regulated activity of Sox5 (TRANSFAC V$SOX5_01 motif; fold difference = 2.29, SE = 1.05, $P = 0.028$) and RORα (TRANSFAC V$RORA2_01 motif; fold difference = 3.00, SE = 1.55, $P = 0.013$) (Figure 2, lower panel); these transcriptional pathways help drive the differentiation of Th17 cells.[26,27]

4 | DISCUSSION

There are marked socioeconomic disparities in the clinical sequelae of childhood asthma.[2–5] To begin characterizing the molecular basis of these disparities in disease control, we performed genome-wide expression profiling of monocytes and T-helper cells from pediatric asthma patients of lower- and higher-SES families. Although the groups had similar disease severity, and other potential confounds were statistically controlled, their transcriptional profiles differed in several notable respects. The monocytes of lower-SES children showed indications of up-regulated anti-microbial and pro-inflammatory activity, as reflected in higher expression of genes involved in monocyte chemotaxis and processing and presentation of antigens.

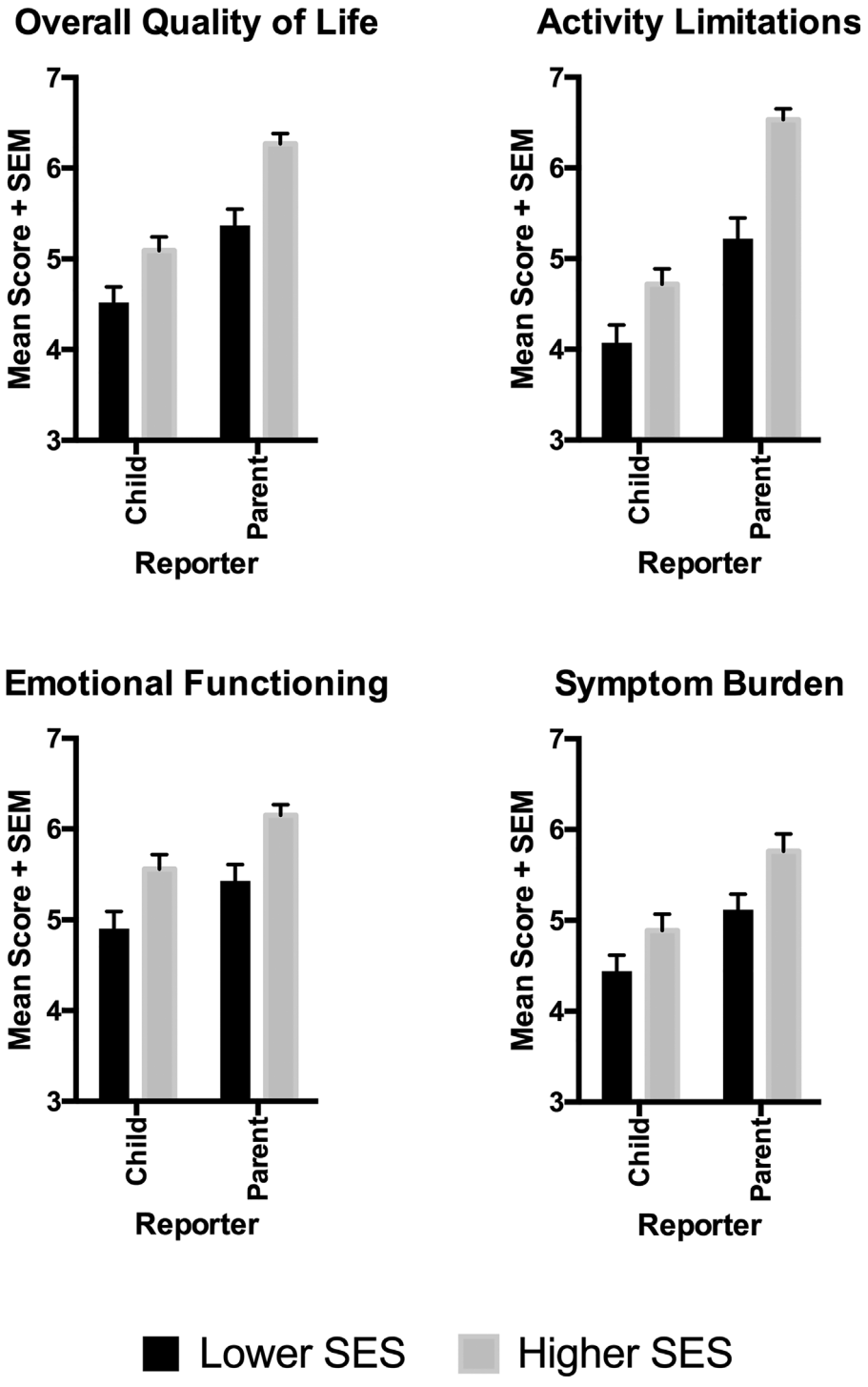

FIGURE 1 Pediatric asthma patients reported on multiple dimensions of their asthma quality of life, and so did one of their patents. Across reporters, children from families of lower socioeconomic status (SES) had worse quality of life than counterparts from higher-SES families

Bioinformatic analyses of response element prevalence implied a role for the transcription factors AP-1 and ELK-1 in orchestrating these differences. These patterns mirror earlier transcriptional studies in healthy adults, which showed higher anti-microbial and pro-inflammatory activity in monocytes of lower-SES individuals.[14,15] The current study supports AP-1 and ELK-1 as the primary transcriptional drivers of such effects in children with asthma, whereas earlier studies of healthy populations indicated a more prominent contribution from NF-κB. To clarify the basis of these differences, a follow-up study comparing healthy and asthmatic youth is needed. In the meantime, the findings here suggest that lower-SES youth may experience worse asthma outcomes partly because of increased monocyte trafficking to the airways and more aggressive clearance of antigens, both of which would presumably amplify downstream

TABLE 2 Differentially expressed transcripts identified in isolated CD14+ cells

Transcript	Adjusted fold difference (lower:higher SES)
Down-regulated in lower-SES children	
HSPA1B	0.602
HSPA1A	0.707
DNAJB1	0.717
HRASLS3	0.740
THBS1	0.744
RPS23	0.745
LOC731682	0.756
SPATA20	0.757
UTS2	0.758
HLA-DQB1	0.774
FAM118A	0.784
RGS1	0.790
HIST1H2BG	0.804
LOC85390	0.809
ACCS	0.818
S100P	0.828
Up-regulated in lower-SES children	
LOC644936	1.696
HLA-DRB5	1.405
LOC728830	1.357
CD9	1.343
LOC729708	1.331
LMNA	1.328
LOC645979	1.313
LOC641768	1.289
LOC441377	1.288
LOC728823	1.282
FOLR3	1.267
CTSG	1.267
HES4	1.263
IFITM3	1.261
HLA-DRB1	1.257
HLA-DRB6	1.256
PROK2 1	0.253
LOC100129650	1.252
AFMID	1.245
LOC646753	1.242
LOC100133823	1.237
MSLN	1.229
LOC644928	1.226
ERAP2	1.226
GSTM2	1.222
CCL2	1.220
LOC442727	1.218
EMP1	1.216
CCL4L1	1.215
LILRA3	1.213
DFNA5	1.213
LOC100129543	1.204
LOC644934	1.203

In addition to SES group, the models also include the following covariates: age, sex, body mass index, asthma severity, and frequency of ICS and SABA use in past week.

lymphocyte effector responses. Consistent with this scenario, there is increasing recognition that innate immune cells, including monocytes, play a role in both acute exacerbations of asthma, and the more chronic airway inflammation that characterizes poorly controlled disease.[12,13]

The groups' T-helper cell profiles also diverged in several regards. Lower-SES children had comparatively reduced expression of the γ-interferon and tumor necrosis factor-α genes, which encode cytokines that orchestrate Type 1 immune responses. These patterns converge with findings in viral-challenge studies, which show that following pathogen exposure, lower-SES individuals have greater susceptibility to upper respiratory viruses.[28,29] Considered alongside evidence that airway viral infections exacerbate asthma,[30] these data suggest the possibility that worse clinical outcomes in lower-SES patients are partly due to compromised Type 1 responses to respiratory pathogens. Also notable in the profiles of lower-SES children were indications of greater T-helper lymphocyte proliferation, differentiation, and activation, which are consistent with patterns observed in a small study of socioeconomic variations in T-cell transcriptional activity.[31] Bioinformatic analyses suggested these disparities were orchestrated by the transcription factors AP-1, GATA, Sox5, and RORα. Although more in-depth functional studies are needed to characterize the significance of these patterns, they provide clues about underlying sources of T-helper cell dysregulation. GATA-3 plays a key role in the functional polarization of T-helper cells, inhibiting Type 1 while enhancing Type 2 cytokine responses.[32] Consistent with a scenario involving excess GATA-3 activity, we found down-regulated expression of the canonical Type 1 cytokines γ-interferon and tumor necrosis factor-α in helper T cells of lower-SES children. Though no differences in Type 2 cytokine expression were observed, past studies have reported that lower-SES children with asthma have exaggerated production of interleukins-4, -5, and -13 following ex vivo stimulation.[5,8,9] The bioinformatic indications of increased Sox5 and RORα signaling are also of interest. These transcription factors play key roles in the maturation and activation of Th17 cells,[26,27] which are involved in neutrophilic inflammation and remodeling of the airways.[33]

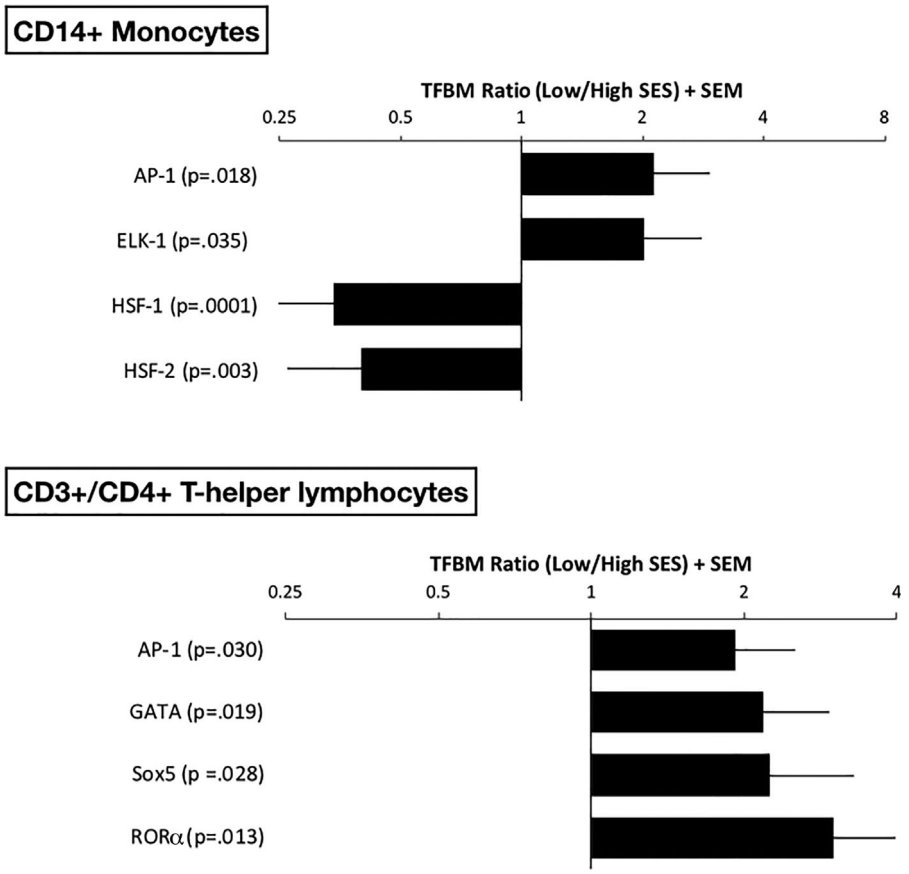

FIGURE 2 Linear models were used to estimate the magnitude of differential gene expression in groups of pediatric asthma patients with lower versus higher socioeconomic status (SES). The models were adjusted for a panel of a priori selected covariates. Genes showing 1.20-fold differential expression between groups served as input into higher-order bioinformatics analyses using the Transcription Factor Element Listening System. This platform quantified the prevalence of transcription factor binding motifs (TFBMs) in promoters of differentially expressed genes. TFBM ratios >1 indicate specified transcriptional pathway is up-regulated with low SES; ratios <1 indicate converse. Upper panel shows findings on CD14+ monocytes, and lower panel shows findings in CD3+/CD4+ T-helper lymphocytes

What mechanisms might underlie the transcriptional disparities between lower- and higher-SES children? There are profound socioeconomic gradients in children's exposure to psychological stressors, as well as irritants, pollutants, allergens, and pathogens that can trigger asthma exacerbations.[7] Our study was not designed to elucidate the relative importance of these exposures in mediating transcriptional disparities. Nevertheless, we did not observe bioinformatic indications of group differences in the activity of transcriptional regimes that convey catecholamine and glucocorticoid signals to the leukocyte genome (for glucocorticoid response elements and CREB response elements, *p*'s ranged from 0.07-0.85). These findings suggest that stress hormones were not critical mediators of the differences observed here. Though based on earlier research, it seems likely that stress-related differences in these hormones' genomic effects come into play once cells have been activated by asthma triggers.[5,34] Lower-SES youth could also have different exposures related to lifestyle factors such as adiposity, smoking, or alcohol use, though we believe those are unlikely to explain the differences here. Only three children reported use of cigarettes and alcohol in the past year, and our models included body mass index as a covariate. Diet could play a role mediating SES differences, and it should be assessed in future research. Generally speaking, the literature suggests that both "social" and "physical" pollutants contribute to socioeconomic disparities in asthma outcomes, and do so through independent and synergistic pathways.[35–37]

When interpreting this study's findings, several limitations should be considered. First, the cross-sectional, extreme-groups design cannot provide inferences about causality. Although our models were adjusted for likely confounders, other factors could plausibly have inflated the associations (eg, genetic variations that cluster within families, and contribute to both parental income and children's health). That being said, experimental studies in animals show that causal effects of SES are biologically plausible; for instance, rodents exposed to early stressors involving deprivation subsequently display heightened susceptibility to airway inflammation and asthma exacerbations.[38] Second, although we defined the study groups based on family income, they also differed on racial identity, with more African-Americans in the lower-SES category. This bias is not unique to our sample, but a reflection of broader racial differences in wealth in the United States. Nevertheless, by including race as a covariate, we minimized its influence here. Third, without a parallel comparison in healthy children, it remains unclear whether the observed SES

TABLE 3 Differentially expressed transcripts identified in isolated CD3+/CD4+ cells

Transcript	Adjusted fold difference (lower:higher SES)
Down-regulated in lower-SES children	
HSPA1B	0.474
HSPA1A	0.579
EGR2	0.625
LOC100008588	0.648
TNF	0.680
HSPA6	0.701
RPS23	0.734
SERPINB6	0.759
CRIP2	0.763
IFNG	0.764
IER3	0.767
HIST2H2AA3	0.770
LOC100132564	0.772
LOC642934	0.776
ANKDD1A	0.784
UTS2	0.788
HIST1H2BG	0.790
LOC729362	0.791
LOC653610	0.795
RASD1	0.797
HIST1H2BD	0.804
RNU5A	0.804
LOC85390	0.808
IPO8	0.809
FAM118A	0.813
HBA1	0.813
PMAIP1	0.817
HBA2	0.818
RHOB	0.820
HBB	0.820
P2RY5	0.822
CCDC58	0.822
LOC731682	0.823
HS.572649	0.825
EGR1	0.829
GADD45G	0.831
LOC644889	0.832
SPATA20	0.833
LOC100008589	0.833
Up-regulated in lower-SES children	
LOC644936	1.653
HLA-DRB5	1.507
HLA-DRB1	1.365
LOC646753	1.346
HLA-DRB6	1.326
LOC650298	1.320
LOC100133823	1.319
LOC642178	1.302
LOC100129650	1.285
CD79A	1.269
LOC644928	1.266
IFITM3	1.261
LOC100131971	1.252
HES4	1.246
RPS26	1.246
MYOM2	1.237
LOC645979	1.236
LOC728823	1.235
LOC100129552	1.230
PPFIBP2	1.228
LOC644934	1.227
LYZ	1.227
FCGBP	1.227
ERAP2	1.225
HS.511717	1.223
GSTM2	1.221
ROBO3	1.211
LOC730415	1.205
GSTM1	1.205
LOC644191	1.204
PI16	1.203
LOC650557	1.203
MIR1978	1.202
IGLL1	1.201

(Continues)

TABLE 3 (Continued)

In addition to SES group, the models also include the following covariates: age, sex, body mass index, asthma severity, and frequency of ICS and SABA use in past week.

differences in transcription are specific to asthma versus a more general characteristic of disadvantaged youth, perhaps arising through differential exposure to toxicants, infections, or stressors. Fourth, given the extreme-groups design, it is not clear how generalizable these results are to middle-income children, who represent the vast majority of the population. Finally, the cells used for transcriptional profiling were from peripheral blood, rather than the airways. Follow-up studies in sputum would strengthen confidence in the findings, particularly if conducted following an allergen challenge.

Despite these limitations, this study serves as a first step towards identifying the molecular origins of socioeconomic disparities in pediatric asthma control. Despite considerable effort, these disparities represent a substantial economic burden and psychosocial challenge for children and their families, and a major contributor to pediatric acute care expenditures.[39] With a deeper understanding of the mechanisms involved, and progress refining multilevel, community-based approaches to intervention,[7,40] there are reasons to be optimistic these gaps will begin closing.

ACKNOWLEDGMENT

The research described here was supported by grants HL108723 and HL122328 from the National Institutes of Health.

CONFLICTS OF INTEREST

None of the authors has a conflict of interest—financial or otherwise—to report in relation to this article's contents.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Miller GE, Chen E, Shalowitz MU, et al. Divergent transcriptional profiles in pediatric asthma patients of low and high socioeconomic status. *Pediatric Pulmonology*. 2018;53:710–719. https://doi.org/10.1002/ppul.23983