Dimensions of Socioeconomic Status and Childhood Asthma Outcomes: Evidence for Distinct Behavioral and Biological Associations

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ABSTRACT

Objectives: The objective of this study was to investigate 2 key dimensions of socioeconomic status (SES)—prestige and resources—and their associations with immune, behavioral, and clinical outcomes in childhood asthma.

Methods: Children ages 9 to 17 years with a physician's diagnosis of asthma ($N = 150$), and one of their parents participated in this study. Children and parents completed interviews and questionnaires about SES (prestige = parent education; resources = family assets), environmental exposures, and clinical asthma measures. Spirometry was conducted to assess children's pulmonary function, and blood was collected to measure cytokine production in response to nonspecific stimulation, allergen-specific stimulation, and microbial stimulation.

Results: Higher scores on both dimensions of childhood SES were associated with better clinical outcomes in children (β's from |.18 to .27|, p values < .05). Higher prestige, but not resources, was associated with better home environment control behaviors and less exposure to smoke (β's from |.21 to .22|, p values < .05). Higher resources, but not prestige, was associated with more favorable immune regulation, as manifest in smaller peripheral blood mononuclear cell (PBMC) T_H1 and T_H2 cytokine responses (β's from −.18 to −.19; p values < .05), and smaller proinflammatory cytokine responses ($\beta = -.19$; $p < .05$) after ex vivo stimulation. Higher resources also were associated with more sensitivity to glucocorticoid inhibition of T_H1 and T_H2 cytokine production (β's from −.18 to −.22; p values < .05).

Conclusions: These results suggest that prestige and resources in childhood family environments have different implications for behavioral and immunological processes relevant to childhood asthma. They also suggest that childhood SES relates to multiple aspects of immunologic regulation of relevance to the pathophysiology of asthma.

Key words: socioeconomic status, childhood, asthma, immune.

INTRODUCTION

Growing up low in socioeconomic status (SES) during childhood puts individuals at greater risk for a number of diseases later in life, including cardiovascular diseases, autoimmune conditions, respiratory diseases, and some cancers (1,2). These associations are generally independent of current adult SES (3,4), suggesting that early childhood environments may be a particularly important period for establishing trajectories of health into adulthood, perhaps through biological programming pathways such as epigenetic alterations and tissue remodeling (1). Low childhood SES also increases risk for pediatric health problems, including asthma, obesity, and injuries (5–7), suggesting that the implications of SES for health begin early in life.

Much of this evidence has focused on population-level associations of SES with health (8,9), although more recent work has seen a growing incorporation of biology into population-health research (10,11). This work has largely been conducted in healthy adults and focused on risks for cardiometabolic disorders. For example, in adults, SES is

IFN = interferon, **IL** = interleukin, **INO** = ionomycin, **ODN** = oligodeoxynucleotides, **PBMC** = peripheral blood mononuclear cells, **PMA** = phorbol 12-myristate 13-acetate, **SES** = socioeconomic status, **TLR** = Toll-like receptor, **TNF** = tumor necrosis factor

SDC Supplemental Content

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associated with epinephrine, norepinephrine, and cortisol (12–14), as well as markers of low-grade inflammation thought to underlie cardiometabolic disorders (15–17). There is also evidence that SES during childhood presages differential activation of biological processes during adulthood, particularly related to inflammation (18–25).

By contrast, little is known about SES and biology during childhood, despite its importance for understanding how early social environments get "under the skin" to affect health across the lifespan (1,26). The work done in childhood has largely focused on cardiovascular risk factors, for example, between SES and childhood cholesterol, insulin resistance, blood pressure, and intima media thickness (27–30).

One piece missing from this literature has been an investigation of mechanistic research on social disparities in clinical populations during childhood. Starting with a disease framework can provide insights toward mechanistically plausible psychobiological models (31) by leveraging knowledge from basic science and focusing on those biological processes clearly implicated in pathogenesis. By asking whether these processes vary with social context, we can begin to identify at what levels biologically childhood SES can get under the skin to shape health outcomes.

Childhood asthma is a disease characterized by reversible inflammation and obstruction of the airways, which arises through bronchial hyper-responsiveness to allergens, infections, and other triggers. In response to these stimuli, T-helper lymphocytes release cytokines, which facilitate downstream effector functions oriented toward eradicating intracellular or extracellular pathogens. Broadly speaking, the former involve cell-mediated responses, enabled by T_H1 cytokines, and the latter involve antibody-mediated responses, enabled by T_H2 cytokines. Basic research on asthma has pointed toward a key role for T_H2 cytokines in the molecular and cellular cascades that give rise to airway inflammation (32,33). For example, the T_H2 cytokines interleukin (IL)-4 and IL-13 facilitate the proliferation and differentiation of B lymphocytes, and the release of immunoglobulin E (IgE) molecules, which dock on mast cells in the airways, causing them to degranulate and release mediators that contribute to early-phase airway constriction and mucus production. The T_H2 cytokine IL-5 recruits eosinophils to the airways and induces them to release late-phase mediators, which contribute to chronic inflammation in asthma. Triggers also cause T-lymphocytes to release T_H1 cytokines like IFN-γ, which mobilize antiviral cellular immune responses, and to some degree counter-regulate T_H2 mediated processes (34). It is important to note that whereas this has been the prevailing model in asthma research, it derives from mouse models of disease and in studies of humans, the T_H1/T_H2 distinction is less clear (35).

In most psychobiological asthma research (36–41), researchers have probed T_H1 and T_H2 cytokine activity by activating lymphocytes ex vivo with nonspecific ligands, such as phorbol 12-myristate 13-acetate (PMA), phytohemagglutinin, and ionomycin (INO). Although these ligands induce lymphocytes to release cytokines, they do not directly engage the T-cell receptor complex. A more physiological approach would entail activating cells with asthma-relevant stimuli that elicit antigen-specific, memory-dependent cytokine responses (42,43). Following this approach, in the present study, we activated peripheral blood mononuclear cells (PBMCs) with 2 common asthma triggers, cockroach antigen and dust mites, as well as a nonspecific mitogen cocktail for comparison to previous research. We then measured production of a panel of T_H1 and T_H2 cytokines, asking how these cytokines varied with SES in an economically diverse sample of children with asthma.

There is also increasing recognition that front-line immune defenses play a central role in the airway pathology that underlies asthma (44,45). Through Toll-like receptors (TLRs), monocytes, macrophages, and dendritic cells recognize conserved molecular patterns associated with pathogens, tissue damage, and necrosis. By producing proinflammatory cytokines like IL-1, IL-6, and tumor necrosis factor (TNF)-α, these cells recruit lymphocytes to the airways and polarize effector responses along the T_H1/T_H2 dimension. Via these pathways, exaggerated inflammatory cytokine responses are thought to contribute to the expression of symptoms in allergies and asthma (46,47). Thus, in the present study, we also considered how SES relates to patterns of proinflammatory cytokine production after stimulation of specific TLRs.

Glucocorticoids play a major role in the immune processes that underlie asthma and the medications used to manage symptoms. Physiologically, cortisol regulates many innate and adaptive immune functions. Although generally considered inhibitory, its physiological effects depend on tissue concentration and phase of the immune response (48). Pharmacologically, synthetic versions of cortisol are used in asthma treatment to attenuate inflammation. However, there are marked individual variations in sensitivity to cortisol's actions, and research shows that chronic stress is associated with lower responsivity to this hormone's anti-inflammatory properties (49–52). Yet none of this research has examined whether cortisol sensitivity might help explain socioeconomic disparities in childhood asthma outcomes. We do so here, focusing on cortisol's ability to modulate T_H1 and T_H2 cytokine production by stimulated PBMCs.

In addition to expanding the scope of immune pathways considered in asthma, we also note that SES itself is a multidimensional construct. One common distinction in the SES literature (across sociology, psychology, economics, and public health) is to differentiate prestige from resources (53–55). Prestige refers to indicators of a person's status or standing within society, and is most frequently measured by parent education (56). In contrast, resources refer to material assets such as the wealth a family has (54,57). Although

the prestige and resources labels connote "status" versus "money," different SES measures may operate in different ways (53,57,58), and these pathways may sometimes depart from the labels. For example, associations of asthma outcomes with resource-based SES might suggest access to higher-quality medical care. In contrast, associations with prestige SES markers such as education might suggest a greater knowledge about the behaviors families must undertake to manage asthma.

Thus, in the present study, we assessed prestige- and resource-based SES and compared their associations with immune processes, health behaviors (environmental control and exposure to smoke), and clinical outcomes (lung functioning, symptoms, and quality of life) in children with asthma. Immunologically, we measured (*a*) PBMC production of T_H1 and T_H2 cytokines after stimulation with specific and generic ligands, (*b*) PBMC production of inflammatory cytokines after stimulation with microbial ligands, and (*c*) the capacity of glucocorticoids to modulate these processes. We hypothesized that children with lower SES would have cells that responded more aggressively to stimulation, and that would be less sensitive to glucocorticoid modulation.

METHOD

Participants

One hundred fifty children of ages 9 to 17 years who were physician-diagnosed with asthma were recruited through one health care system, NorthShore University HealthSystem, and one federally qualified health center, Erie Family Health Center. Children came to the research laboratory with one parent to complete the measures described below. Families were required to be fluent in English, and children had to be free of acute respiratory illness at the time of the visit and have no other chronic physical illnesses other than asthma. Children gave written assent, and parents provided written consent. This study was approved by the Northwestern, NorthShore, and Erie institutional review boards. Data were collected between July 2013 and December 2014. Demographic information about the sample is found in Table 1.

Measures

Childhood Socioeconomic Status (SES)

Childhood SES was measured along dimensions of prestige and resources by asking at the household level about parents' education and family assets, respectively. For prestige SES, parents were asked the number of years of education they and their partner (if they had one) had attained. The higher of the two was used to represent parent educational attainment as a continuous variable (consistent with previous research: (7,59). We used this measure, as it is the most frequently used prestige marker for SES (56). For resource SES, parents were asked about the amount of assets (family savings, investments, etc.) that their family could easily convert to liquid cash in an emergency. Parents responded with a dollar amount, and this variable was log transformed before analyses to normalize distribution. We used this measure to be consistent with previous approaches to measuring resources in other psychoneuroimmunology studies (39,60) (also see www.macses.ucsf.edu).

Cytokine Production

We measured stimulated cytokine secretion by PBMCs. Although airway cells would better reflect activity at the site of disease, obtaining them requires a highly invasive procedure that would be inappropriate for children without a clinical indication. For that reason, pediatric asthma studies have often relied on PBMC assays, and research shows they correspond to measures taken via bronchoalveolar lavage, and to eosinophil count and disease severity (61,62). Antecubital blood was drawn into BD Cell Preparation Tubes (Becton Dickinson, Franklin Lakes, NJ) containing sodium heparin, and PBMCs were isolated by density-gradient centrifugation according to the manufacturer's instructions, and dispensed into 12-well culture plates in the presence of several different mitogen configurations. First, to measure T_H1 versus T_H2 cytokine production after nonspecific stimulation, we incubated 0.5×10^6 PBMCs with 25 ng/mL of PMA (Sigma-Aldrich, St. Louis, MO) + 1 μg/mL of INO (Sigma-Aldrich, St. Louis, MO) for 24 hours at 37°C in 5% CO_2, similar to previous studies (39,40,63). An unstimulated well with the same number of PBMCs but no mitogen was cultured under the same conditions. At the end of the incubation, supernatants were harvested by centrifugation and frozen at −80°C until assayed in batch via electrochemiluminescence on a SECTOR Imager 2400A (Meso Scale Discovery, MSD, Rockville, MD). This instrument gives accurate, sensitive multiplex readouts across a wide dynamic range (64). We made use of MSD's Human T_H1/T_H2 7-Plex Tissue Culture Kit, which measures both T_H2 (IL-2, IL-4, IL-5, and IL-13) and Th-1 (IFN-γ and IL-10) cytokines in parallel. Mean interassay coefficients of variation ranged from 2.67% to 4.86%. Cytokine responses were quantified by subtracting values in the unstimulated wells from those in the PMA/INO wells.

To measure T_H1/T_H2 cytokine production in response to asthma-relevant ligands, 5×10^6 PBMCs were dispensed into wells containing either 10 μg/mL of cockroach extract (50:50 mixture of American and German cockroach; Greer, Lenoir, NC) or 10 μg/mL of dust mite extract (50:50 mixture of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*; Greer, Lenoir, NC), and incubated for 72 hours at 37°C in

TABLE 1. Descriptive Information About the Sample ($N = 150$)

	Mean	SD	% (*N*)
Child age	14.12	2.07	
Sex, male			57 (86)
Ethnicity, white			49 (74)
Family savings[a]	30,000		
Parent's education (highest)	17.14	2.78	
Beta agonist			48 (72)
Inhaled corticosteroid			45 (67)
Exposed to smoke, days/wk	0.70	1.42	
Environmental control	3.90	2.97	
PEF (% predicted)	97.34	16.72	
Asthma control	20.84	3.59	
Asthma quality of life	5.18	1.10	
Days missed of school	1.55	3.20	
Courses of oral steroids	0.31	0.65	

PEF = peak expiratory flow.

[a] Because of the skewed distribution of family savings, median value in dollars is presented here. Parent's education refers to highest number of years of education of either parent. Beta agonist and inhaled corticosteroid use refers to the percent of children who have taken that medication in the past week. Environmental control is on a 1 to 9 scale. Asthma control ranges from 5 to 25. Asthma quality of life ranges from 1 to 7. Days missed of school and oral steroid courses are over the past 6 months. Values are not included for cytokine composites because they all have a mean of 0 and a standard deviation close to 1 (given how scoring was done).

5% CO_2, similar to previous study protocols (43,65). An unstimulated well was also included on the plate. Supernatants were assayed in batch using the same MSD platform and reagents as previously described, capturing both T_H2 (IL-2, IL-4, IL-5, and IL-13) and T_H1 (IFN-γ, IL-10) cytokine production. Mean interassay coefficients of variation were 1.98% to 4.24%. As previously shown, values in unstimulated wells were subtracted from values in active wells before analysis.

To measure proinflammatory cytokine production from TLR stimulation, 0.5×10^6 PBMCs were dispensed into plates containing either 0.1 ng/mL of lipopolysaccharide (LPS; a molecule found on gram-negative bacteria that stimulates the TLR-4 pathway; Invivogen, San Diego, CA) or 10 μg/mL of CpG oligodeoxynucleotides (ODN; single-stranded bacterial DNA, which stimulates the TLR-9 pathway; Invivogen, San Diego, CA) and incubated for 24 hours at 37°C in 5% CO_2, similar to previous studies (21,43). An unstimulated well was also included on the plate. Supernatants were assayed in batch for cytokine production using the Sector Imager, and a custom MSD Human Pro-Inflammatory Tissue Culture kit (Rockville, MD), which measured IL-1β, IL-6, and TNF-α in parallel. Interassay coefficients of variation were 3.47% to 10.27%, and previously shown, unstimulated values were subtracted out before analysis. See Supplemental Digital Content 1, http://links.lww.com/PSYMED/A323, for more details regarding the frequency of values below detection cutoffs for each of the individual cytokines.

Glucocorticoid Sensitivity

To measure sensitivity to glucocorticoid modulation, 0.5×10^6 PBMCs were coincubated with 25 ng/mL of PMA, 1 μg/mL INO and 1.38×10^{-6} mol/L hydrocortisone (Sigma-Aldrich, St. Louis, MO) for 24 hours at 37°C in 5% CO_2, similar to previous studies (49,50). An unstimulated well was also included on the plate. Supernatants were assayed in batch using the MSD T_H1/T_H2 kit, as previously shown, and unstimulated values were subtracted out before analysis. At the dose used, cortisol suppresses production of T_H1 and T_H2 cytokines, so higher values can be interpreted as reflecting greater insensitivity to glucocorticoid inhibition.

Environmental Control

The Family Asthma Management System Scale was used to probe family behaviors around controlling environmental exposures (66). This is a semistructured interview that probes exposures to environmental triggers (e.g., smoking, pets) and efforts to improve the environment (e.g., air filters). Interviewers ask parents and children to describe the home environment, and based on concrete behaviors reported, make a rating of environmental control on a 9-point scale. Validity for this interview has been established through associations with asthma symptoms and functional impairment (66). It has been used in children as young as 7, and inter-rater reliability (Intraclass correlation coefficient) for our team was .98. Higher scores on this interview indicate better environmental control.

We also asked children to report on a primary exposure relevant to asthma: smoke. Because only 3 children (2%) reported ever having smoked a cigarette in their life, we focused on exposure to smoke as an asthma-relevant behavior. Children were asked about the number of days per week that they were exposed to second-hand cigarette, cigar, or pipe smoke.

Asthma Clinical Outcomes

Pulmonary function was assessed in the laboratory using spirometry (Microloop, CareFusion, Basingstoke, UK), according to American Thoracic Society guidelines (67). Measures were taken at least 4 hours after the last use of a short-acting bronchodilator, and at least 24 hours after the use of a long-acting bronchodilator, following the protocols of a multisite clinical asthma trial (68). Peak expiratory flow percentile was calculated as a percentage of predicted values, based on child age, sex, ethnicity, and height (69).

To assess symptoms, the Asthma Control Test (70,71) was completed by parents. It is a 5-item questionnaire that assesses the frequency and severity of children's asthma symptoms over a 1-month period. Reliability for this questionnaire is high (.84), and validity has been established through associations with ratings of asthma specialists' ratings of control (70). The Asthma Control Test is a commonly used measure in clinical settings. Higher numbers indicate more well-controlled asthma.

Parents were also asked about the number of days of school their child missed because of asthma in the past 6 months as well the number of courses of oral steroids their child had taken in the past 6 months.

Children's quality of life was measured using the Pediatric Asthma Quality of Life Questionnaire, a 23-item measure rated on a 7-point scale, completed by children (72). Measures have high reliability (Intraclass correlation coefficient: .85–.94) and validity in being associated with peak flow and beta agonist use in patients with asthma (72). The child version is appropriate for ages 7 and older, with higher scores indicating higher quality of life.

Statistical Analyses

Variables that were not normally distributed were first log-transformed. Principal components analysis was first used to reduce the number of cytokine variables and hence the number of analyses conducted. Varimax rotation was used when 2 or more factors emerged. Statistical analyses were performed using SPSS version 22. Multiple regression analyses were conducted in which asthma-related outcomes were regressed upon predictor variables. In the first step, covariates of child age, sex, ethnicity, inhaled corticosteroid use (yes/no), and beta agonist use (yes/no) were included. In the second step, the family SES variable (either parent's education or family assets) was included.

RESULTS

Preliminary Analyses

Table 1 shows descriptive information about the sample. Prestige and resource SES were correlated at $r = .41$, $p < .01$.

Principal components analyses were conducted to determine whether cytokine responses could be aggregated. For assays involving proinflammatory cytokine production from TLR stimulation, single-factor solutions emerged for both the LPS and ODN wells, with the principal component explaining 67.8% to 86.1% of the variance. Factor loadings ranged from .78 to .95 (for IL-1β), from .80 to .93 (for IL-6), and from .89 to .94 (for TNF-α). Accordingly, we created composite indicators for each condition by standardizing then averaging values of IL-1β, IL-6, and TNF-α.

For the T_H1 versus T_H2 cytokines, principal components analyses of both the cockroach and dust mite stimulations revealed a 2-factor solution. Factor 1 accounted for 51.6% to 53.4% of the variance, and Factor 2 accounted for 24.7% to 25.4% of the variance. Factor 1 corresponded to the T_H2 cytokines and was comprised of IL-2 (factor loadings ranging from .86 to .88), IL-4 (factor loadings from .77 to .87), IL-5 (factor loadings from .90 to .93), and IL-13 (factor loadings from .90 to .95). Factor 2 corresponded to the T_H1 cytokines and was comprised of IFN-γ (factor loadings, .70–.84) and IL-10 (factor loadings, .61–.80). Given that the empirical factor loadings were consistent with the theoretical T_H1 versus T_H2 distinction, we created composites reflecting primarily T_H1 and T_H2 cytokines

responses, separately for each ligand. Again, cytokine values were standardized and averaged.

Prestige-Based SES and Asthma Outcomes

Table 2 shows a summary of findings.

Immune Measures

Prestige SES was not associated with either T_H1 or T_H2 responses to PMA/INO stimulation (unstandardized *b*'s ranging from −.018 to −.020, SEs from .029 to .031, *p* values ranging from .516 to .531). Prestige SES also was not associated with T_H1 or T_H2 responses to either cockroach or dust mite stimulation (b's ranging from .003 to .025, SEs from .025 to .028, *p* values ranging from .347 to .917). Finally, prestige SES was not associated with either T_H1 or T_H2 responses to PMA/INO + cortisol stimulation (*b*'s ranging from .003 to .004, SE's = .029, *p* values ranging from .889 to .929).

Higher prestige SES was associated with smaller proinflammatory cytokine response to ODN stimulation (b = −.056, SE = .026, p = .033, ΔR^2 = .032), but not with responses to LPS stimulation (b = −.016, SE = .030, p = .580).

TABLE 2. Associations of Prestige and Resource-Based Childhood SES Measures With Asthma Immune, Behavioral, and Clinical Outcomes (N = 150)

	Prestige SES	Resource SES
	β	β
Immune (cytokine production)		
Nonspecific stimulation		
PMA/INO: T_H1	−.057	−.180*
PMA/INO: T_H2	−.055	−.190*
Innate immune stimulation		
LPS: proinflammatory	−.049	.089
ODN: proinflammatory	−.183*	−.238*
Adaptive immune stimulation		
Cockroach: T_H1	.027	−.102
Cockroach: T_H2	.009	.021
Dustmite: T_H1	.036	.026
Dustmite: T_H2	.077	.055
Glucocorticoid sensitivity		
PMA/INO + Cort: T_H1	.012	−.207*
PMA/INO + Cort: T_H2	.008	−.198*
Behavioral		
Environmental control	.212**	.073
Exposure to smoke	−.216**	.018
Clinical		
PEF percentile	.044	.201*
Asthma control test	.292***	.221**
Asthma quality of life	.244**	.231**
School days missed	−.171*	−.201*
Courses of oral steroids	−.201*	−.111

β = standardized beta; Prestige SES = parent education; Resource SES = family assets; PMA = phorbol 12-myristate 13-acetate; INO = ionomycin; LPS = lipopolysaccharide; ODN = oligodeoxynucleotides; Cort = cortisol.

* $p < .05$, ** $p \leq .01$, *** $p < .001$.

Immune variables list type of stimulation followed by type of cytokine measured. All regression analyses control for child age, sex, ethnicity, beta agonist use, and inhaled corticosteroid use.

Health Behaviors

In contrast to the patterns with immune measures, higher prestige SES was associated with better interview ratings of home environment control (b = .225, SE = .085, p = .009, ΔR^2 = .044). Higher prestige SES also was associated with fewer weekly exposures to smoke in children (b = −.018, SE = .007, p = .009, ΔR^2 = .046).

Clinical Outcomes

Higher prestige SES was associated with indicators of better clinical outcomes. These indicators included better asthma control (b = .370, SE = .100, $p < .001$, ΔR^2 = .083), fewer days of school missed because of asthma (b = −.021, SE = .011, p = .048, ΔR^2 = .026), fewer courses of oral steroids over a 6-month period (b = −.011, SE = .005, p = .014, ΔR^2 = .039), and higher child quality of life (b = .097, SE = .032, p = .003, ΔR^2 = .058).

Resource-Based SES and Asthma Outcomes

Table 2 shows for a summary of the findings below.

Immune Measures

Higher resource-based SES was associated with smaller T_H2 (b = −.094, SE = .045, p = .037, ΔR^2 = .032) and T_H1 (b = −.095, SE = .048, p = .048, ΔR^2 = .029) cytokine responses to nonspecific stimulation with PMA/INO. In contrast, resource SES was not associated with T_H1 or T_H2 responses to the asthma-specific ligands, cockroach and dust mite antigens (*b*'s ranging from −.049 to .028, SE's from .040-.044, *p* values ranging from .232 to .811).

With respect to TLR stimulation, higher resource SES was associated with smaller proinflammatory cytokine responses to ODN stimulation (b = −.111, SE = .045, p = .014, ΔR^2 = .045).

Finally, with respect to glucocorticoid sensitivity, higher resource SES was associated with smaller T_H2 (b = −.095, SE = .042, p = .028, ΔR^2 = .038) and T_H1 responses (b = −.101, SE = .042, p = .019, ΔR^2 = .041) to PMA/INO + cortisol stimulation. Both patterns indicate a greater sensitivity to glucocorticoid inhibitory signaling in higher SES children.

Health Behaviors

In contrast to the patterns with immune measures, resource SES was not associated with home environment control

(b = .123, SE = .139, p = .378) or with exposure to smoke in children (b = .002, SE = .012, p = .837).

Clinical Outcomes

Higher resource SES was associated with better clinical outcomes, including higher lung function (b = 1.919, SE = .949, p = .045, ΔR^2 = .028), better asthma control b = .445, SE = .165, p = .008, ΔR^2 = .047), fewer days of school missed because of asthma (b = −.039, SE = .016, p = .014, ΔR^2 = .039), and better child quality of life (b = .144, SE = .051, p = .006, ΔR^2 = .051).

Associations between prestige and resource SES with individual cytokine responses are shown in the online Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A323.

DISCUSSION

These analyses reveal several novel findings about the associations between SES and asthma in childhood. First, lower levels of resource-based SES and prestige-based SES both covaried with worse clinical outcomes, including worse pulmonary function, more disease symptoms and related school absences, and lower quality of life. Second, whereas both SES dimensions were associated with clinical outcomes, they had distinct relationships with behavioral and biological factors relevant to asthma. Prestige, but not resources, was associated with asthma management behaviors related to environmental control and exposure to smoke. In contrast, resources, but not prestige, were consistently associated with profiles of cytokine production. That is, lower resource-based SES was associated with larger T_H2 and T_H1 responses to nonspecific (PMA/INO) stimulation of PBMCs and lower sensitivity to the inhibitory properties of glucocorticoids. Lower resource-based SES also covaried with larger proinflammatory cytokine responses to ODN stimulation. Neither SES dimension was associated with T_H1 or T_H2 responses to dust mite or cockroach antigen.

The associations of lower SES with greater production of T_H2 cytokines in response to PMA/INO are consistent with previous research (39,40) and demonstrate that the PBMCs of children with asthma from lower SES families exhibit greater responsivity to a controlled ex vivo exposure relative to children from higher SES families. Lower SES also was associated with greater production of $T_H1$cytokines. T_H1 cells may be helping to facilitate the recruitment of T_H2 cells to the airways, thus serving to exacerbate responses to allergen exposures (73). This pattern is consistent with previous research that has found relations between psychosocial factors and both T_H1 and T_H2 responses in asthma (41).

Contrary to predictions, we found no associations of PBMC cytokine production in response to cockroach or dust mite stimulation with childhood SES. Although we had anticipated that these triggers would provide a more asthma-relevant exposure, it is possible that differential sensitization or current exposure to these allergens across children obscured patterns of associations with SES. Although we chose two of the most common allergens implicated in asthma, an allergen-specific stimulation approach might need to first test children for sensitization to allergens, and then use a specific allergen that each child is responsive to; however, although this approach has the advantage of being patient-centered, it could complicate comparisons across children (given the difficulty in creating equivalent doses of exposure across allergens).

We found that lower SES children with asthma also displayed greater PBMC proinflammatory cytokine production to ODN, a form of bacterial DNA that stimulates the TLR-9 pathway. These findings suggest that low childhood SES may increase the inflammatory response to microbial stimuli, consistent with previous research focusing on other forms of childhood adversity (42,43,50). Because of the historical emphasis on T- and B-lymphocytes in asthma, less attention has been paid to innate immune cells, like monocytes, macrophages, and dendritic cells. However, research increasingly has emphasized the role of these cells as environmental sensors, which detect microbes, pollutants, and other asthma triggers, and orchestrate the subsequent response by T- and B-lymphocytes (44,45). The current study's findings further support the value of studying innate responses in asthma.

Lastly, we found evidence that SES indicators covaried with glucocorticoid sensitivity. To the extent they had lower SES, children's PBMCs produced larger quantities of $T_H2$and T_H1 cytokines when coincubated with cortisol and PMA/INO. These findings suggest that the PBMCs of lower SES children with asthma are showing a reduced capacity to mitigate T_H1 and T_H2 cytokine production in the context of inhibitory signals from cortisol. These findings are consistent with previous work on other childhood adversities and glucocorticoid sensitivity (49,50). Taken together, the overall patterns suggest 2 different immunologic mechanisms (larger cytokine responses to microbial stimuli, and reduced sensitivity to inhibitory hormonal signaling) that may be shaped by the experience of low childhood SES and that may have implications for diseases such as asthma.

The fact that associations with immune measures emerged more strongly for resource SES rather than prestige SES is intriguing and provides suggestions about the mechanisms by which these dimensions of status might affect health. For example, it may be the case that greater resources allow families access to better health care (58) (better doctors, specialists, newer medications) that in turn ameliorate airway inflammation and obstruction. Alternatively, greater resources may shape early-life exposures and sensitizations

to allergens that in turn are linked to current cytokine production profiles. Psychologically, greater resources make also make it easier for families to deal with life stressors (being able to eliminate stressors, facilitating coping with stressors), and given the associations of stress with asthma-relevant inflammation (74–76), the ability to reduce the impact of life stressors might in turn reduce inflammation. In contrast, the lack of associations with prestige SES suggests that education alone, perhaps reflecting knowledge about asthma (77), is not sufficient to affect inflammatory processes in asthma.

In contrast, prestige, but not resources, was associated with behavioral factors relevant to asthma control. That is, higher prestige SES was associated with having better environmental control in the home and with children being less exposed to second-hand smoke. In this case, it may be that behaviors related to environmental controls are shaped more by one's knowledge about asthma and communications with health care providers (which may be linked to parent' education levels (57,77)) than they are by the financial resources one has. For example, a family has to have been told about and understand the links between dust mites and asthma before they are likely to take significant steps in cleaning to reduce household dust exposure. The dimension-specific patterns observed in this study are also consistent with previous research that has found more robust associations of income (rather than education) with inflammatory markers (16) and are consistent with work that demonstrates that income is more strongly related to the progression of disease or mortality (which may be related to immune measures in a population with preexisting disease) than is education (58,78).

Limitations to the present study include the cross-sectional nature of this study, meaning that conclusions about causality and directionality cannot be drawn. Future studies that are longitudinal in nature would allow researchers to track trajectories of childhood SES, behavioral and biological factors, and asthma outcomes to determine how they inter-relate over time. This type of design would help to determine whether cytokine production patterns precede changes in asthma impairment and severity over time, or whether they are a reflection of underlying severity. In addition, a design like this would help answer questions about sensitive periods, that is, whether the influence of SES on asthma outcomes varies across periods of childhood. Furthermore, future studies would benefit from incorporating more comprehensive measures of SES (multiple prestige and multiple resource measures) to determine more precisely which types of SES markers are related to childhood asthma outcomes. The fact that associations in the present study emerged for ODN, but not LPS, suggests that links between SES and proinflammatory cytokine production in asthma may be more tenuous, and further work needs to be done in this area to determine if these results are replicable. The present study sought to establish relationships between different types of childhood SES measures and a host of immunologic, behavioral, and clinical asthma outcomes; although it was beyond the scope of the present study, future research should conduct more in depth investigations into the possible psychosocial mediators that are shaped by low childhood SES circumstances and that are relevant to asthma, including psychological states such as depression or anxiety, as well as social network factors such as family stress. In addition, the present study was limited to identifying effects linked to SES; however, low SES may serve in part as a proxy for other social environment exposures, such as traumatic life experiences, violence, and/or poor parent mental health, and hence future research should test whether other types of childhood adversities have similar associations with childhood asthma outcomes.

In summary, this article contributes to our understanding of the links between childhood SES and inflammatory mechanisms in asthma. We demonstrate that both prestige- and resource-based childhood SES are associated with clinical asthma outcomes, but only prestige SES is associated with asthma-relevant behaviors, whereas resource SES is more consistently associated with cytokine production. Resource SES displayed associations with both T_H2 and T_H1 cytokine responses to nonspecific stimulation, with microbial-stimulated proinflammatory cytokine production, and with glucocorticoid sensitivity. These results indicate multiple immunologic processes involved in the pathophysiology of childhood asthma that seem to be subject to regulation by childhood socioeconomic environments, suggesting the potential importance of targeting these childhood circumstances as one way of altering the course of chronic inflammatory conditions such as asthma over the lifespan.

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