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Parents' Childhood Socioeconomic Circumstances are Associated with their Children's Asthma Outcomes

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Abstract

Background—Previous literature documents associations between low socioeconomic status (SES) and poor health outcomes, including asthma. However, this literature has largely focused on the effects of current family circumstances.

Objective—To test an intergenerational hypothesis, that the childhood SES that parents experience will be associated with asthma outcomes in their children, independent of effects of current family SES. Secondly, to test whether this association is in part due to difficulties in current parent-child relationships.

Methods—Observational study, whereby 150 parents were interviewed about their childhood SES, and their children (physician-diagnosed with asthma, ages 9–17) were interviewed about current family stress. Asthma control was assessed by parent- and child-report (primary outcome), and blood was collected from children to measure cytokine production relevant to asthma (secondary outcomes).

Results—To the degree that parents had lower childhood SES, their offspring showed worse asthma outcomes across multiple indicators. This included lower asthma control scores (parent and child-report, p's<.05), and greater stimulated production of Th-2 and Th-1 cytokines by peripheral blood mononuclear cells (PBMC) (p's<.05). These associations were independent of current family SES. Mediation analyses were consistent with a scenario wherein parents with low childhood SES had current family relationships that were more stressful, and these difficulties in turn related to worse asthma control and greater cytokine production in children.

Conclusions—These results suggest the potential 'long reach' of low socioeconomic status across generations, and the importance of expanding theories of how the social environment can affect childhood asthma to include characteristics of earlier generations.

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Keywords

socioeconomic status; family stress; asthma; childhood

INTRODUCTION

Low socioeconomic status (SES) has robust associations with a number of adverse health outcomes[1,2], including asthma[3,4]. For example, children with asthma who come from low SES backgrounds are more likely to visit the emergency department, to be hospitalized for asthma, and to experience greater functional impairment (e.g., greater activity limitations) because of asthma[5–10]. In children with asthma, lower SES also is associated with a tendency to express inflammatory profiles indicative of poorly controlled asthma, including higher eosinophil counts and larger Th-2 cytokine responses following *in vitro* stimulation of peripheral blood mononuclear cells (PBMC)[11,12].

The majority of the research in this area has focused on the effects of current SES on health. However, in more recent years there has been growing interest in the idea of intergenerational effects – that is, the idea that environments experienced in one generation could have effects on the health of subsequent generations[13,14]. These effects have been primarily demonstrated using experimental manipulations in animal models with outcomes such as birthweight, obesity, diabetes, cardiovascular risk, and behaviors, whereby the effects of an environmental condition (e.g., changes to diet) performed on the grandparent generation are evident in the grandoffspring generation (even when the grandoffspring do not experience the same environment as their grandparents)[15–18]. These types of findings raise the intriguing question of whether it is possible for parents' own childhood SES environments to affect asthma outcomes in their children, above and beyond the effects of current SES.

In human populations, some preliminary evidence exists in support of the idea of intergenerational transmission of environmental effects. For example, women who were pregnant during the Dutch Hunger Winter of World War II had grandchildren with greater adiposity and poorer health compared to women whose pregnancy occurred outside the window of the Dutch famine[19]. Other evidence includes the finding that parents who grew up with low childhood SES were more likely to have children with higher blood pressure and higher levels of an inflammatory biomarker that predicts cardiovascular disease, C reactive protein, even after controlling for current SES[20], as well as to have children with lower birthweights[21]. In addition, grandmother smoking during pregnancy has been found to predict an increased risk of asthma in grandchildren, independent of maternal smoking during pregnancy[22]. In the present study, we tested whether the childhood SES that parents grew up with would forecast their children's level of asthma control (primary outcome), independent of the effects of current family SES. Secondarily, we investigated whether parents' childhood SES would be linked to immune responses relevant to asthma. Asthma is an inflammatory disease, characterized by T-helper cell release of cytokines in response to allergens, infections, and other triggers. A key role has been proposed for the release of Th-2 cytokines in airway inflammation[23,24]. In addition, the release of Th-1 cytokines linked to

anti-viral cellular responses may also be relevant to asthma[25]. Alternatively, front-line immune defenses involved in innate immunity, such as Toll-like receptors that recognize pathogens and produce pro-inflammatory cytokines, are also thought to contribute to asthma exacerbations[26,27]. Because each of these represent a different immunologic pathway to asthma, we investigated separately the PBMC production of Th-2, Th-1, and pro-inflammatory cytokines in response to *in vitro* stimulation, in order to document plausible biological correlates of intergenerational SES effects.

Why might parents' early life circumstances predict asthma outcomes in their children? One psychosocial explanation may be related to stress in the parent-child relationship. If parents grow up in low SES environments, they are on average more likely to have been exposed to conflictual, harsh, and unsupportive environments[28–30]. Parents who grow up in these environments may then be more likely to engage in punitive and inconsistent parenting behaviors as adults[31]. In turn, factors such as dysfunctional family interactions, parenting difficulties, family conflict, and lack of parent support have been associated with atopic illness, asthma diagnosis, asthma symptoms and mortality, and poorer pulmonary function in children[32–35]. The idea that stressful environments experienced early in a parent's life can impact offspring behavior is also seen in animal models (mice) whereby manipulations of childhood stress (e.g., social instability) in a parent generation produce behavioral changes (e.g., anxiety) in offspring mice[36,37].

Thus the goals of the present study were three-fold. We first tested whether parents who experienced lower childhood SES environments were more likely to have children with worse asthma outcomes, as reflected in parent- and child-reports of asthma control (primary outcome) and secondarily, to have children with greater stimulated production of cytokines implicated in asthma. Second, to determine whether these associations simply reflect the inter-generational continuity of poverty, we examined whether they persisted following statistical adjustment for families' current SES. Lastly, we used statistical modeling to examine the plausibility of a mediational scenario, wherein parents with low childhood SES have more stressful current family relationships, with these difficulties in turn fostering worse child asthma outcomes.

METHOD

Participants

One hundred and fifty children ages 9–17, physician-diagnosed with asthma, were recruited through one health care system, NorthShore University Health System, and one federally-qualified health center, Erie Family Health Center (hence all families in this study had access to health care). See Online Supplement. Children came to the research center with one parent between July 2013 and December 2014 to complete the assessments 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. Participants had current asthma, with 96% having a current beta agonist prescription, 71% having a current inhaled corticosteroid prescription, and all had a recent office visit for asthma. Children gave written assent and parents provided written consent. This study was approved by the Northwestern, NorthShore, and Erie IRBs.

Measures

Socioeconomic status (SES)—SES was measured by interviewing parents about family resources. Parents' childhood SES was assessed via early childhood home ownership (home ownership is often used as a measure childhood SES, given that other types of assets can be difficult for adults to retrospectively recall). Parents were asked whether their family owned or rented their home during their first 3 years of life. Thus renting a home constituted the lower SES group, and owning a home constituted the higher SES group. The accuracy and predictive validity of this question has been previously established, as well as the importance of SES during the early childhood years[38,39]. Current family SES was measured by asking parents about the amount of assets (family savings, investments, etc.) that their family could easily convert to liquid cash in an emergency. This measure is consistent with previous approaches to measuring family resources[11,40] (also see www.macses.ucsf.edu).

Family relationship stress—Family relationship stress was determined by interviewing children using the University of California Los Angeles Life Stress Interview[41,42]. This interview probes chronic stress within the family over the past 6 months, focusing on conflict between family members, trust, and support. Interviewers rate the extent of a participant's family relationship stress on a 1–5 scale (including .5 ratings), with higher numbers reflecting more severe and persistent family relationship difficulties (e.g., greater conflict, less trust, and lower support). Reliability and validity for this interview have been demonstrated in children as young as 8[42,43]. Interrater reliability (intraclass correlation coefficient) across interviewers was .93.

Asthma control—The Asthma Control Test[44,45] is a 5-item questionnaire that assesses asthma symptoms, use of rescue medications, and the effects of asthma on daily functioning over the previous 4 weeks. Reliability for this questionnaire is high (.84), and validity has been established through asthma specialists' ratings of control[44]. This measure is commonly used in clinical settings, and has parent- and child-report versions. Higher numbers indicate more well-controlled asthma (possible range: 5–25).

Immunologic measures - cytokine production—We measured stimulated cytokine secretion by PBMCs. Although airway cells would better reflect activity at the site of disease, obtaining them requires an invasive procedure difficult for children without a clinical indication. For that reason, pediatric asthma studies often rely on assessments of PBMC activity, which correlate with data obtained via bronchoalveolar lavage specimens, and also with eosinophil counts and disease severity[46,47]. 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 manufacturer instructions, and dispensed into the wells of culture plates in the presence of different mitogens. We focused on one common mitogen known to generate Th-1 and Th-2 cytokine release: here we incubated 0.5×10^6 PBMCs with 25ng/mL of phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich, St. Louis, MO) + 1ug/mL of ionomycin (INO; Sigma-Aldrich, St. Louis, MO) for 24 hours at 37°C in 5% CO_2, similar to previous studies[11,12,48]. An unstimulated well was prepared containing the same number of PBMCs but no mitogen, and 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). This instrument gives accurate, sensitive multiplex readouts across a wide dynamic range[49]. We made use of MSD's Human Th-1/Th-2 7-Plex Tissue Culture Kit, which measures both Th-2 (IL-2, IL-4, IL-5, and IL-13) and Th-1 (IFN-γ, IL-10) cytokines in parallel. Mean inter-assay coefficients of variation ranged from 1.50–3.64%. Cytokine responses were quantified by subtracting values in the unstimulated wells from those in the PMA/INO wells.

To measure pro-inflammatory cytokine production in response to TLR stimulation, we utilized one microbial and one viral analogue ligand. 0.5×10^6 PBMCs were dispensed into plates containing either 0.1ng/mL of lipopolysaccharide (LPS, a molecule found on Gram-negative bacteria that stimulates the Toll Like Receptor (TLR)-4 pathway; Invivogen, San Diego, CA) or 100ug/mL of Poly I:C (double stranded RNA, which stimulates the TLR-3 pathway; Invivogen, San Diego, CA) and incubated for 24 hours at 37°C in 5% CO_2, similar to previous studies[50,51]. 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, which measured IL-1β, IL-6, and TNF-α in parallel. Interassay coefficients of variation were 3.49–8.68%, and as per above, unstimulated values were subtracted out prior to analysis.

Statistical Analyses

Statistical analyses involved 4 sets of tests: (1) associations of parents' childhood SES with children's asthma control and immune outcomes; (2) associations of parents' childhood SES with current family relationship stress; (3) associations of current family relationship stress with child asthma control and immune outcomes; and (4) statistical mediation analyses of the pathway: parents' childhood SES → current family relationship stress → child asthma outcomes. For (1) and (2), analyses of covariance (ANCOVAs) were conducted, given the dichotomous nature of the parent childhood SES variable. For (3), multiple regression analyses were conducted, given the continuous nature of the family stress variable. Child age, gender, ethnicity (White vs. other), use of beta agonists, and use of inhaled corticosteroids (number of days in the past week) were included as covariates. We note that rather than including whether the child has a current prescription for medication as a covariate (given that 96% were on a beta agonist so there would be little variability in this measure), we included instead the number of days each medication was used in the past week as a proxy for current medication adherence/usage. In a second set of analyses, current SES was added to the above models to test whether the effects of parent childhood SES persisted over and above the effects of current SES. For (4), we tested the significance of the indirect effect using statistical mediation analyses with nonparametric bootstrapping to obtain the bias corrected and accelerated confidence intervals of indirect effects, as recommended by Preacher and colleagues[52]. Confidence intervals that do not include 0 indicate statistically significant indirect pathways. Although the study was observational, and hence cannot determine causality, this statistic tells us whether the data are consistent with a mediation explanation that parents' childhood SES operates through current family relationship stress to affect children's asthma.

RESULTS

See Table 1 for descriptive information about the sample. Note that parents' childhood SES and current family SES were correlated, r=.23, p=.006. However, 37% of the sample moved in SES grouping over time (i.e., parents living in a rented home during childhood but then parents being above the median in current SES for the sample, or parents living in a home their family owned during childhood but then parents being below the median in current SES for the sample). These patterns suggest that SES is not entirely stable across generations, and hence that the findings below are not solely a function of remaining persistently low in SES over time.

Parents' Childhood SES → Current Family Stress → Child Asthma Control

Parent Childhood SES and Child Asthma Control—ANCOVA analyses revealed significant differences in children's asthma control by parents' childhood SES. These disparities were evident in both parents' [F(1, 142)=6.65, p=.011], and children's reports [F(1,143)=3.927, p=.037]. As Table 2 and Figure 1 reveal, parents who grew up in lower SES circumstances [parent: M=20.11, 95% CI: 19.34–20.87; child: M=19.31, CI: 18.58–20.04] had children with poorer asthma control compared to those who grew up under higher SES circumstances [parent: M=21.47, CI: 20.76–22.17; child: M=20.31, CI:19.64–20.99]. Cohen's d statistic is often used to express the magnitude of an effect, that is, how large group differences are in standard deviation units. The d values for the above effects range from .33–.43.

When current SES was added to these models, the group differences noted above remained significant [parent report: F(1,136)=6.16, p=.014. Low SES M=20.06, CI:19.27–20.84. High SES M=21.40, CI:20.68–22.13; child report: F(1,137)=4.44, p=.037. Low SES M=19.27, CI:18.53–20.00. High SES M=20.34, CI:19.66–21.02]. These results indicate that associations of parents' childhood SES with offspring asthma control are independent of families' current SES circumstances.

Parent Childhood SES and Current Family Relationship Stress—ANCOVA analyses revealed a significant difference in current family relationship stress by parents' childhood SES [F(1,144)=7.75, p=.006. Low SES M=2.37, CI:2.20–2.54. High SES M=2.04, CI:1.89–2.20]. Cohen's d for the effect size was .45. If parents grew up in lower SES circumstances, their current family relationships were rated as more stressful. When current SES was added into the model, this association remained significant [F(1,138)=7.68, p=.006. Low SES M=2.39, CI:2.21–2.56. High SES M=2.06, CI:1.90–2.22], indicating that the effect of parents' childhood SES on current family stress was independent of current family SES.

Current Family Relationship Stress and Child Asthma Control—Regression analyses revealed significant associations of current family relationship stress with asthma control as reported by parents (standardized β=−.17, p=.048) and children (β= −.22, p=.006). These patterns indicated that higher levels of family relationship stress were associated with poorer asthma control in children. See Table 3. When including current SES as a

covariate, the association with parent report ACT was: β= −.16, p=.07, and the association with child report ACT was: β= −.23, p=.005.

Family Relationship Stress as a Pathway?—We conducted statistical mediation analyses to test whether current family relationship stress mediated the relationship between low parent childhood SES and child asthma control. Analyses revealed a significant mediated, or indirect, effect of −.20 for parent-report of asthma control [confidence interval, CI: −.60, −.01]. There was also a significant indirect effect of −.34 for child-report of asthma control [CI: −.88, −.07]. These findings are consistent with a scenario wherein the quality of current family relationships serves as one pathway linking parents' early life circumstances to their children's current asthma control.

Parent Childhood SES → Current Family Stress → Child Cytokine Production

For cytokine data, distributions of each cytokine were reviewed, and those that were not normally distributed were log transformed. Factor analyses revealed that cytokine responses could be aggregated into a Th-2 factor (IL-2, 4, 5, and 13), a Th-1 factor (IFN-γ, IL-10) for PMA/INO stimulation, and into a single pro-inflammatory factor (IL-1β, IL-6, TNF-α) for LPS and Poly I:C[53]. Results of these factor analyses were used to reduce the number of dependent variables by combining conceptually and empirically related cytokines. Composite indicators were created by standardizing and averaging individual cytokine values (unweighted). The analyses below utilize these cytokine composites.

Parent Childhood SES and Child Cytokine Production—ANCOVA analyses revealed significant associations between parents' childhood SES and children's PMBC production of both Th-2 [F(1,134)=4.77, p=.031, Cohen's d=.38. Low SES M=.18, CI: −.04 – .40. High SES M=−.15, CI: −.36 – .05] and Th-1 cytokines [F(1,134)=10.19, p=.002, Cohen's d=.54. Low SES M=.27, CI:.04–.50. High SES M=−.23, CI: −.44 to −.02] following stimulation with PMA/INO. For pro-inflammatory cytokine responses to Poly I:C, the association was [F(1,130)=2.81, p=.096, Cohen's d=.29. Low SES M=.14, CI: −.10 – .37. High SES M=−.13, CI: −.35 – .08]. There were no differences in cytokine response to LPS [F(1,130)=0.92, p=.339, d=.16. Low SES M=.08, CI: −.15 – .31. High SES M=−.07, CI: −.28 – .14]. These patterns indicated that parents who grew up in lower SES circumstances had children whose PBMCs exhibited larger Th-2 and Th-1 cytokine responses. See Table 2 and Figure 2.

When current SES was added to these models, the above patterns remained the same [Th-2: F(1,129)=5.72, p=.018. Low SES M=.21, CI:.00–.44. High SES M=−.15, CI: −.35 – .05; Th-1: F(1,129)=11.25, p=.001. Low SES M=.31, CI:.08–.54. High SES M=−.22, CI: −.44 to −.01; Poly I:C pro-inflammatory cytokines: F(1,125)=2.56, p=.11. Low SES M=.13, CI: −.11 – .37. High SES M=−.14, CI: −.36 – .08].

Parent Childhood SES and Current Family Relationship Stress—As reported above, there was a significant association of parents' childhood SES with current family relationship stress [F(1,144)=7.75, p=.006], that persisted after controlling for current SES [F(1,138)=7.68, p=.006].

Current Family Relationship Stress and Child Cytokine Production—Regression analyses revealed significant associations between current family relationship stress and pro-inflammatory cytokine responses to Poly I:C stimulation (β=.19, p=.035). Higher levels of family relationship stress were associated with larger pro-inflammatory cytokine responses in the PBMCs of children. Even after current SES was added as a covariate, the above finding remained significant (β=.21, p=.028). No associations were found with Th-1 or Th-2 cytokines. See Table 3.

Family Relationship Stress as a Pathway?—Statistical mediation analyses revealed a significant mediated, or indirect, effect of .05 for pro-inflammatory cytokine responses to Poly I:C with a bootstrapped 95% CI of [.0037, .1789]. These findings are consistent with the explanation that the quality of current family relationships serves as one pathway linking parents' early life circumstances to their children's pro-inflammatory cytokine responses.

Sensitivity Analyses

To test the robustness of associations of parents' childhood SES with child asthma outcomes, we repeated the above analyses controlling for a different current family SES variable (parent education instead of family assets). When years of parent education was added to the models, the results were as follows: [parent ACT: F(1,141)=5.85, p=.02; child ACT: F(1,142)=3.60, p=.06; PIC: F(1,129)=2.71, p=.10; PMA/INO Th-2: F(1,133)=4.60, p=.03; PMA/INO Th-1: F(1,133)=9.96, p=.002]. These results indicate that, with the exception of child ACT (which went from p=.037 to p=.06), associations of parents' childhood SES with offspring asthma outcomes are robust to type of current SES measure used as a covariate.

DISCUSSION

The results of this study provide early evidence that parents' socioeconomic conditions when they were children are related to the health of the next generation: their own children's asthma outcomes. Specifically, as compared to parents who grew up under better socioeconomic conditions, parents who grew up in lower SES households were more likely to have children with poorer asthma control. Secondarily, as we explored asthma-relevant immunologic measures, we found that when parents grew up in lower SES households, their children were more likely to have PBMCs that exhibited larger Th-2 and Th-1 cytokine responses to PMA/INO stimulation *in vitro*. Moreover, these findings were independent of families' current SES circumstances.

These findings add to a growing body of literature on SES across the lifecourse, which has demonstrated that not only is current family SES related to numerous health outcomes including asthma[3,8,54,55], but also that childhood SES predicts health outcomes later in adulthood, independent of current SES[56–59]. In the present study, we demonstrate the value of expanding lifecourse models[60,61] to also include a consideration of environments from previous generations.

The present study's findings also extend previous human studies on the intergenerational effects of poverty to a clinical disease context. Previous work has documented

intergenerational effects of individuals experiencing poverty or associated conditions during early childhood or *in utero* on future generations' (these individuals' children) risk factor profiles, including adiposity and blood pressure[19,20]. In addition, intervention work has demonstrated that providing nutrition supplements to individuals during their early childhood or *in utero* years results in these individuals later in life having children with greater birthweights and who are taller[62,63]. To our knowledge, however, no research has yet documented intergenerational effects of low SES on clinical outcomes in populations with chronic diseases.

Why would the childhood socioeconomic circumstances of parents be associated with asthma outcomes in their children? While there may be numerous explanations (e.g., epigenetic modifications[13,14]), in this study, we focused on one psychosocial possibility related to family stress. Parents who grow up in low SES households are more likely to experience frequent family conflict, harsh parenting, and poorer quality family interactions as children[28,29,64]. These stressful childhood experiences are believed to engender behavioral tendencies that persist across the lifecourse, including subsequently being more likely to develop abrasive social relationships as adults (involving greater conflict and rejection, less support and warmth)[59]. Thus parents who grow up under low SES circumstances may be more likely to have conflictual and less supportive and trusting relationships with their children. The present study's findings support this notion, documenting associations of low parent childhood SES with greater current family relationship stress, above and beyond effects of current family SES.

In turn, among children with asthma, experiencing family relationships that are more conflictual and less supportive is associated with poorer asthma outcomes. For example, previous research has shown that parenting difficulties when children were young predicted a subsequent diagnosis of childhood asthma[34]. In addition, family dysfunction and parent-child conflict discriminated children with severe asthma who died from asthma from children with severe asthma who did not[35]. Family relationships also have been associated with immune markers in children with asthma. For example, in another sample of children with asthma, greater family relationship stress was associated with greater Th-2 cytokine responses to PMA/INO stimulation *in vitro*[11]. In addition, lower levels of parent support have been associated with higher levels of eosinophil cationic protein (a cytotoxic protein released from activated eosinophils, considered a marker of airway inflammation) and with reduced PBMC sensitivity to glucocorticoid inhibition in children with asthma[65]. The present study's findings add to this literature in documenting that greater family stress was related to both poorer child asthma control and greater pro-inflammatory cytokine responses to PBMC stimulation in children with asthma. We note that although both parent childhood SES and current family stress were related to cytokine responses, they were associated with different markers (Th-1 and Th-2 responses for the former, and pro-inflammatory responses for the latter), suggesting that different social exposures may affect different immunologic processes that have implications for asthma control. In addition, because these measures are taken in peripheral blood, local immune processes in the airways may serve as more proximal mediators to clinical outcomes.

In addition, statistical mediation analyses documented support for the indirect pathway–that is, the pathways from low parent childhood SES to greater current family relationship stress to poorer child asthma control and to larger pro-inflammatory cytokine responses were significant. Although this study cannot make claims about causality because it was not experimental, these findings are nonetheless consistent with an explanation that one reason why parents' childhood SES is associated with their child's asthma outcomes is because of the difficulties in current family relationships that parents and children in these households are experiencing.

Limitations to the present study include the design being a cross-sectional observational study. As such, we are unable to determine causality or directionality. In addition, the sample size is small by epidemiological standards, though it is comparable to other studies that have investigated links between psychosocial factors and inflammatory processes in clinical populations[66–68]. Future studies that are able to recruit larger cohorts and incorporate longitudinal designs that follow children's trajectories over time, and as well, across multiple generations, would be ideal for testing intergenerational hypotheses and for obtaining more reliable estimates of effect sizes. In addition, the assessment of parents' childhood SES was retrospective and relied on parent-report and hence could be subject to recall biases. For example, it is possible that those parents with children whose asthma is more severe are more likely to recall more difficult childhoods, and that this accounts for the associations we see in these analyses. While this is entirely possible and hence a limitation of the present study, we also note that: 1) our measure of childhood SES was a single dichotomous variable that is concrete and easy for many to recall (home ownership). Previous research has documented that subjective perceptions of socioeconomic conditions are more prone to recall biases than objective questions, and as well, that objective childhood socioeconomic status questions can be recalled with a relatively high degree of accuracy[69,70]; 2) previous research has demonstrated that personality characteristics that are known to bias memories do not affect associations between retrospective childhood SES (as measured by home ownership) and adult health[38], suggesting that childhood home ownership may not be as susceptible to such recall biases; and 3) in order to avoid retrospective reporting for a study with a design such as this one, we would have needed an approximately 40-year longitudinal follow-up (given that the average age of parents was 45). While we strongly advocate the investigation of clinical cohorts with this length of follow-up, until these can be funded, we may need to rely on retrospective reports of childhood SES for intergenerational studies of asthma such as this one. In addition, having greater details about parents' childhood psychosocial environment in future studies would be informative. Finally, studies that are able to test additional pathways related to intergenerational transmission, including epigenetics and physical environment exposures, would help with the development of conceptual models of how parent early life environments can get transmitted to children.

In sum, these findings suggest that efforts to understand how the social environment can affect childhood asthma may need to expand to a consideration of periods before the child was born. Over and above a family's current SES, the childhood SES environments that parents grew up in predict their children's asthma control and secondarily, cytokine responses. These findings suggest the potential 'long reach' of low socioeconomic status

across generations, and imply that efforts to ameliorate asthma disparities in our society may have to go beyond improving the current socioeconomic circumstances of families to addressing the social circumstances that children grow up in and the potential effects of these environments across generations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SES	socioeconomic status
PBMC	peripheral blood mononuclear cells
IL	interleukin
IFN	interferon
PMA/INO	phorbol 12-myristate 13-acetate/ionomycin
LPS	lipopolysaccharide
ACT	Asthma Control Test

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Key messages

- Parents who grew up in lower socioeconomic status (SES) backgrounds were more likely to have children with worse asthma outcomes, independent of current family SES.
- These effects are partially explained by more stressful current family relationships.
- These findings suggest that theories of how the social environment can affect childhood asthma may need to be expanded to include influences from earlier generations.

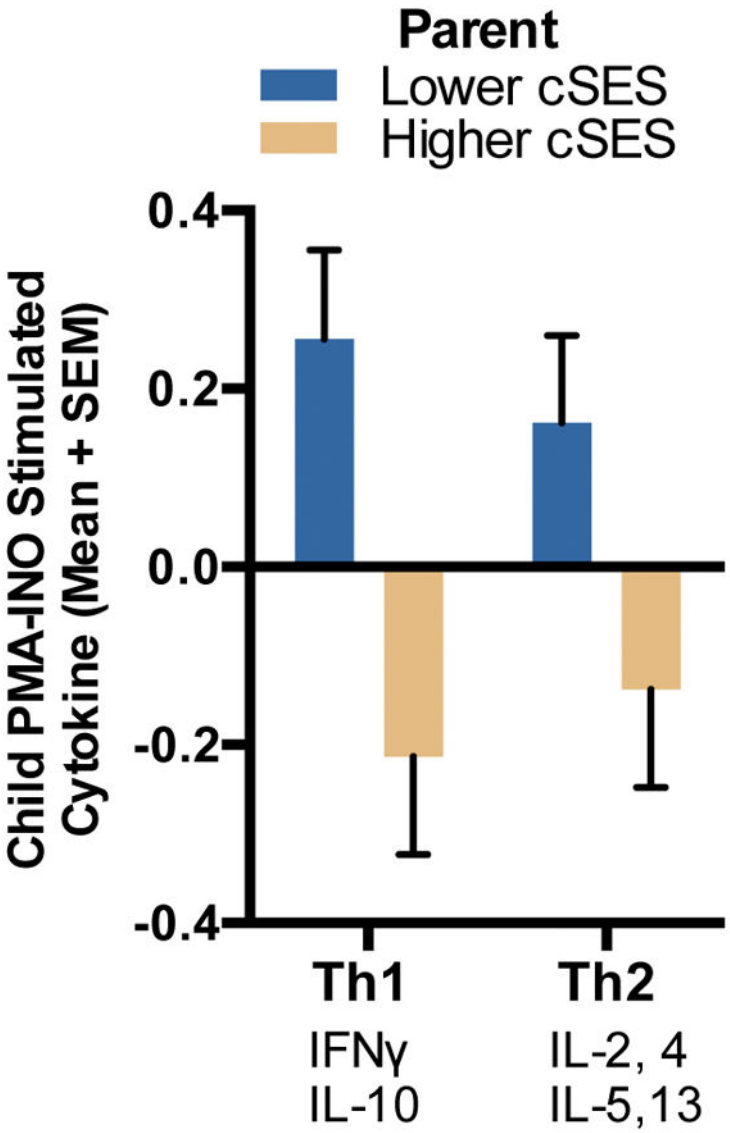

Figure 1.
Children's asthma control by parents' childhood SES (cSES). Bars are shown by both child report on the Asthma Control Test, as well as parent report on the Asthma Control Test.

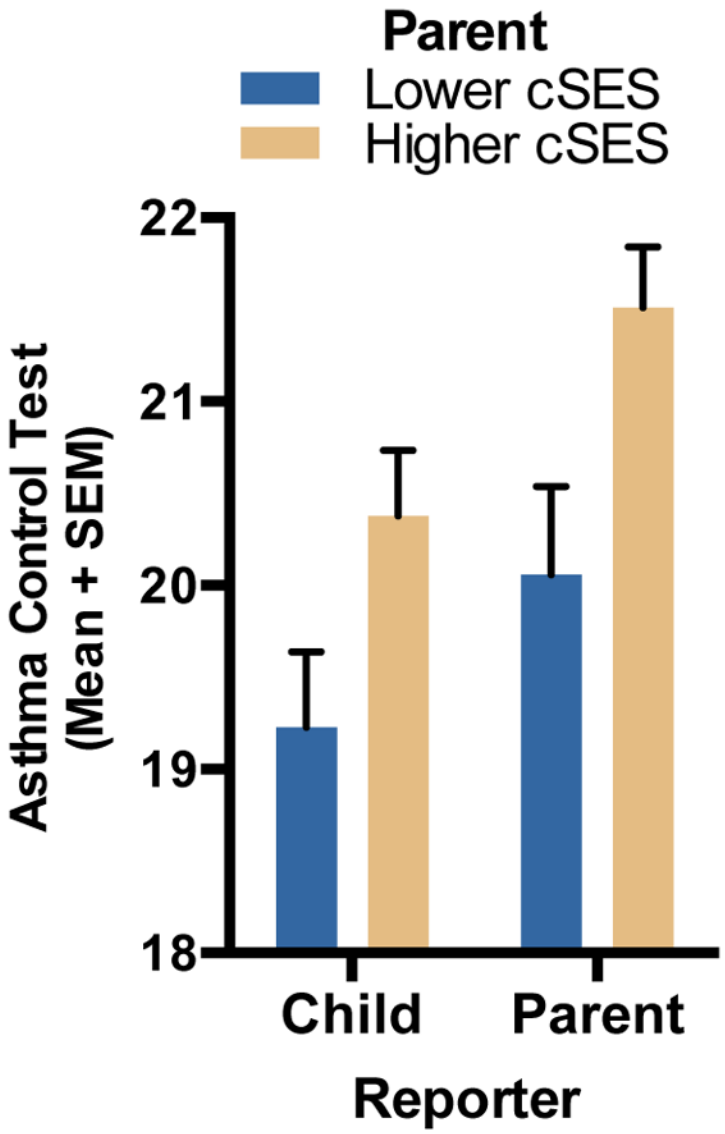

Figure 2.

Parents' childhood SES (cSES) and children's cytokine production in response to stimulation with PMA/INO (25ng/mL/1ug/mL). Bars are shown for both Th1 and Th2 cytokine responses. Cytokine values are standardized and aggregated into composites.

Table 1

Descriptive information about sample

	M	SD	%
Child age	14.12	2.07	
Gender – male			57
Ethnicity			
Caucasian			49
African American			25
Asian			13
Hispanic			11
Other			2
Beta agonist			96
Inhaled corticosteroid			71
Parent childhood SES – rent			46
Current family SES	5.00	2.74	
Family stress	2.19	0.76	
Asthma control (Child report)	20.84	3.54	
Asthma control (Parent report)	19.85	3.34	
Poly I:C	−0.01	0.94	
LPS	0.00	0.91	
PMA/INO (Th-1)	0.00	0.94	
PMA/INO (Th-2)	0.00	0.90	

Note: Beta agonist and inhaled corticosteroid use refers to the % who have a current prescription for that medication. Current family SES ranges from 1–9, with a 5 corresponding to $20,000-$49,999. Family stress ranges from 1–5. Asthma control ranges from 5–25. LPS=lipopolysaccharide. PMA/INO = phorbol myristate acetate/ionomycin. Cytokine production is represented by composite indicators derived from factor analyses. They include a Th-2 factor (IL-2, 4, 5, and 13), a Th-1 factor (IFN-γ, IL-10), and a pro-inflammatory factor (IL-1β, IL-6, TNF-α). In all cases, values are corrected for non-specific production of each cytokine, then standardized and aggregated into composites.

Table 2

ANCOVA analyses of parents' childhood SES predicting child asthma clinical and immune outcomes.

	Low Parent SES (n=69)		High Parent SES (n=81)			
	M	SE	M	SE	F	p
Asthma control						
Parent report	20.11	.38	21.47	.36	6.66	.011
Child report	19.31	.37	20.31	.34	3.93	.049
Cytokine production						
Poly I:C (innate)	0.14	.12	−0.13	.11	2.81	.096
LPS (innate)	0.08	.12	−0.07	.11	0.92	.339
PMA/INO (Th-1)	0.27	.12	−0.23	.10	10.19	.002
PMA/INO (Th-2)	0.18	.11	−0.15	.10	4.77	.031

Note: LPS=lipopolysaccharide. PMA/INO = phorbol myristate acetate/ionomycin. Cytokine production is represented by composite indicators derived from factor analyses. They include a Th-2 factor (IL-2, 4, 5, and 13), a Th-1 factor (IFN-γ, IL-10), and a pro-inflammatory factor (IL-1β, IL-6, TNF-α). In all cases, values are corrected for non-specific production of each cytokine, then standardized and aggregated into composites. Models include the covariates child age, gender, ethnicity, and usage of beta agonists and inhaled corticosteroids, with M and SE representing adjusted values.

Table 3

Regression analyses of current family relationship stress predicting child asthma immune and clinical outcomes.

	B	Standard Error	ΔR2	p
Asthma control				
Parent report	−.81	.40	.026	.048
Child report	−.96	.35	.043	.006
Cytokine production				
Poly I:C (innate)	.23	.11	.033	.035
LPS (innate)	.12	.11	.008	.298
PMA/INO (Th-1)	.15	.11	.013	.186
PMA/INO (Th-2)	.09	.11	.005	.434

Note: Current family relationship stress is coded on a 1–5 scale, with higher numbers indicating greater family stress. B=unstandardized b coefficient. LPS = lipopolysaccharide. PMA/INO = phorbol myristate acetate/ionomycin. Cytokine production is represented by composite indicators derived from factor analyses. They include a Th-2 factor (IL-2, 4, 5, and 13), a Th-1 factor (IFN-γ, IL-10), and a pro-inflammatory factor (IL-1β, IL-6, TNF-α). In all cases, values are corrected for non-specific production of each cytokine, then standardized and aggregated into composites. Models include the covariates child age, gender, ethnicity, and usage of beta agonists and inhaled corticosteroids.