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Associations Between Spontaneous Parental Perspective-Taking and Stimulated Cytokine Responses in Children with Asthma

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Abstract

Objectives—Cognitive empathy in parents—reflecting the extent to which one considers the perspectives and emotions of others—is hypothesized to contribute to family social environments in ways that affect youths' physical health. Using a novel assessment technique for cognitive empathy, the current study examined associations between spontaneous parental perspective-taking and key inflammatory processes implicated in pediatric asthma.

Methods—130 children (ages 9–17) with physician-diagnosed asthma, along with one parent, participated in the current study. Parents completed an interview from which statements of perspective-taking were coded and youths provided blood samples.

Results—Youths whose parents demonstrated greater spontaneous perspective-taking during the interview had cells that mounted smaller inflammatory responses to stimulation by non-specific, asthma-specific, and viral analogue ligands, as well as cells that showed greater sensitivity to the anti-inflammatory effects of glucocorticoids. These results were not accounted for by parental warmth or parent or youth depressive symptoms, nor by covariates of race, age, gender, parental education level, use of asthma medications over the past week, or asthma severity.

Conclusions—These findings suggest that parental perspective-taking may have implications for biological processes relevant to childhood asthma.

Keywords

inflammation; empathy; health; family; perspective-taking

Early family environments are critical developmental contexts for youth health, not only because they influence crucial health behaviors (e.g., Lau, Quadrel, & Hartman, 1990; Morrongiello, Corbett, & Bellissimo, 2008), but also because psychosocial characteristics of families can shape physiological processes in ways that affect youths' health across the lifespan. For example, individuals raised in risky family environments characterized by family discord and stress show higher rates of illnesses in childhood (Gottman & Katz, 1989; Repetti, Taylor, & Seeman, 2002), as well as greater risk for heart disease, lung disease, cancer, and liver disease in adulthood (Felitti et al., 1998). Similarly, a study of undergraduates found that men who rated themselves as having a negative relationship with one of their parents in early life were twice as likely to have a diagnosed disease 35 years later than those with neutral or positive relationships (Russek & Schwartz, 1997).

Although previous research seeking to explain these associations has focused primarily on behavioral dimensions of parenting like expressions of warmth or use of harsh discipline (Carroll et al., 2013), the dispositional psychological traits of parents may also affect the parenting strategies they adopt, and, in turn, may likewise contribute to health outcomes in children. For instance, mothers' trait-level positive emotionality has been associated with greater warmth and supportiveness during mother-infant interactions, while lower parental emotional stability has been related to greater use of negative discipline (Mangelsdorf, Gunnar, Kestenbaum, Lang, & Andreas, 1990; Prinzie et al., 2004).

In the current study, we propose that cognitive aspects of empathy may represent an important parental dispositional trait relevant to children's physical health. Here, empathy refers to the trait tendencies of a person to adopt the perspectives of others (cognitive empathy) and to feel concern about another's suffering (affective empathy) (Davis, 1983). By facilitating awareness of their children's needs, cognitive empathy may encourage parents to be more attuned and responsive in their caregiving (Dix, 1992). Parents who more easily take the perspectives of others might be more inclined to anticipate the effects of their actions on their children and to adjust behaviors accordingly. In turn, this sensitivity may result in a more harmonious family environment that then relates to the functioning of physiological systems that are altered by stress.

One key physiological process linked to family environments is inflammation. For example, exposures to abuse or maltreatment during childhood have been linked to higher levels of circulating C-reactive protein (CRP) in adulthood (Danese et al., 2009; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Matthews, Chang, Thurston, & Bromberger, 2014). Moreover, experimental evidence has found that a parenting-focused intervention in an at-risk population of African American youth reduced six biomarkers of low-grade inflammation in the children (Miller, Brody, Yu, & Chen, 2014), strengthening causal inferences regarding family relationships and children's inflammation. Finally, one previous study found that in a sample of medically healthy children, higher parental cognitive and affective empathy assessed by self-report questionnaire was linked to lower levels of CRP in children (Manczak, DeLongis, & Chen, 2016). In the present study, we asked the question of whether similar associations with parental perspective-taking exist within clinical populations and when using a novel measure of spontaneous cognitive empathy.

Pediatric Asthma

Pediatric asthma is one of the most common chronic diseases of childhood (National Center for Health Statistics (U.S.). Division of Health Interview Statistics, 2013) and is characterized by inflammation of the airways in response to allergens and other triggers. Briefly, exposure to antigens, such as dust mites or molds, activates T helper (Th) cells. Th-1 cells initiate cellular immune responses and help to mobilize antiviral responses by secreting proteins known as cytokines, such as interferon-gamma (IFN –γ). Th-2 cells initiate humoral immune responses and include the secretion of cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), which promote processes that result in airway constriction and the production of mucus. In asthma, although Th-2 pathways (and adaptive immunity) are generally the focus of research, exaggerated proinflammatory responses associated with the innate immune system are thought to also contribute to allergic symptoms and disease responses (Jackson et al., 2008; Sigurs et al., 2005). This includes the activity of pro-inflammatory biomarkers such as IL-6 and tumor necrosis factor-alpha (TNF-α).

In addition, inflammatory processes are regulated by glucocorticoids, such as cortisol, which are steroidal hormones that in part serve to dampen inflammatory responses and as well, contribute to metabolic functioning (Busillo & Cidlowski, 2013). Previous work has demonstrated that prolonged exposure to psychological stressors can result in reduced sensitivity to the anti-inflammatory signaling of glucocorticoids (Miller & Chen, 2010; Miller, Gaudin, Zysk, & Chen, 2009; Rohleder, Marin, Ma, & Miller, 2009). Given that synthetic inhaled corticosteroids are commonly used as a first-line treatment for asthma (National Heart, Lung, and Blood Institute, 2002), cortisol sensitivity represents another important biological process to study among children with asthma. These processes are generally studied in humans by creating *in vitro* analogues of how children's immune systems would respond in the presence of triggers under controlled conditions by extracting children's blood cells, culturing them with ligands that stimulate target pathways, and then measuring the amounts of cytokines that result from this exposure (e.g., Bauer et al., 2000; Kang et al., 1997; Waage & Bakke, 1988). Although in the real world, there are many factors that contribute to asthma symptoms and severity, an *in vitro* provides a theoretically meaningful biological model by more cleanly isolating one's tendency to react to asthma triggers with heightened inflammatory responses. Using this paradigm, then, a clinical sample of children with asthma provides a relevant, important test of links between parental perspective-taking and inflammatory processes in children.

Assessment of Perspective-Taking

Thus far, parental empathy has most commonly been measured using self-report questionnaires, such as the Interpersonal Reactivity Index (Davis, 1983), which assesses both cognitive and affective dimensions of empathy. One limitation to this approach, however, is that it may be subject to biased or inaccurate reporting, such as when respondents are influenced by the social desirability of their answers (Van de Mortel, 2008). A different type of assessment would be to look for evidence of spontaneous empathy in parents' actions or words, which might also have greater ecological validity indicating how

empathic processes operate within families. Consequently, the current work sought to code evidence of parents' perspective-taking through interviews as parents discussed personal life experiences (Chen, McLean, & Miller, 2015; McAdams et al., 2004). (Affective dimensions of empathy, such as emotional concern, depend on nonobvious internal experiences and are not as readily visible in narrative discussions.) The rationale was that an interview format would allow parents' natural styles and values to be revealed. Spontaneously considering the perspectives of others would indicate that empathy-relevant processes are automatic and engrained for these parents and would more closely reflect important protective processes as they might be expressed or experienced within the families of children at risk.

The Current Study

The present study sought to test whether spontaneous parental perspective-taking—as captured during interviews with parents about challenging life experiences—would relate to inflammatory processes in a sample of youths diagnosed with asthma. We predicted that greater perspective-taking would relate to smaller cytokine production in children with asthma across a variety of ligands that stimulate both innate and adaptive immune responses, as well as greater glucocorticoid sensitivity. In addition, we hypothesized that these associations would be specific to parental perspective-taking and would not be better accounted for by parental warmth or by parent or youth depressive symptoms.

Method

Participants

One hundred fifty children ages 9–17 who had physician-diagnosed asthma were recruited into a study of health disparities through one health care system and one federally-qualified health care center. One parent participated with each child. Families were required to be fluent in English, and children were required to be free of acute respiratory illness at the time of the visit. This study was approved by Northwestern University's, North Shore Health System's, and Erie Family Health Center's Institutional Review Boards. Twenty dyads were dropped from the current study analyses due to a failure to obtain blood samples (n=2), interview data (n=17), or demographic information (n=1), resulting in a final sample of 130 parent-child dyads (65 mother-son dyads, 49 mother-daughter dyads, 10 father-son dyads, and 6 father-daughter dyads). Youths were on average 14.0 years old (*SD*=2.1) and parents were on average 45.6 years old (*SD*=6.2). Sixty two percent of youths were Caucasian, 26% were African American, 13% were Asian, 12% were Hispanic, and 2% were Native American/Native Alaskan/Native Hawaiian, with participants able to endorse multiple ethnicities. Parents had on average 16.2 years of education, with a range of 12–25 years. On average, children took beta-agonist medication 1.41 days in the past week (*SD*=2.01) and inhaled corticosteroid medication 2.39 days in the past week (*SD*=3.01). Dyads who were retained did not differ on the variables of race, age, gender, medication use, or parental education from dyads who were dropped from analyses due to missing data.

Procedure

During the baseline laboratory visit, parents and youths provided written informed consent and assent and supplied demographic information. Parents and youths jointly reported on asthma medication use. Youths completed a self-report questionnaire of perceived parental warmth and completed a blood draw. Parents completed a semi-structured interview to assess perspective-taking, described in more detail below.

Measures

Parental Perspective-Taking—Parents completed the Life Story Challenge Interview, a semi-structured interview developed for the current study, based on the "key scene" section of the Life Story Interview by McAdams (2008). Parents were asked to select two moments from their lives that they remembered clearly in which they experienced some sort of challenge or struggle. They were asked to described the scene and discuss what they were thinking and feeling, as well as any ways in which they dealt with the experience. Following this, they were asked to reflect on how going through the experience affected their outlook on life as well as what their experiences might say about who they were as a person. They were instructed to first select one memory that involved a challenge or struggle relating to their family and then to select any other challenge or struggle from their adult life for the second scene. Common examples of challenges included the death of a loved one, losing a job, and marital difficulties. These interviews were audio-recorded and then transcribed verbatim. (See Table 1 for complete interview prompts).

Using the transcribed interviews, each memory was coded for the extent to which the parent showed evidence of cognitive aspects of empathy (in the form of perspective-taking) during their discussion, with each experience rated on a 3-point scale (0–2) for the extent to which the participant discussed the perspectives, viewpoints, or motivations of others involved in the challenging experience. Here, participant responses had to demonstrate that they were moving beyond their own thoughts and feelings to acknowledge the ways in which events may be perceived by, or affect, another. Scenes that did not acknowledge perspectives of others received a score of 0, scenes that mentioned, but did not elaborate on the perspectives of others received a score of 1, and scenes that provide extensive consideration of another person's perspective received a score of 2. Importantly, parents were never prompted to consider the experiences of others during this interview, so any evidence of perspective-taking may be seen as occurring naturally and spontaneously. A total of 257 memories were provided.

All interviews were coded by the first author and ninety-four memories (approximately 37%) were double coded by a trained research assistant to establish the reliability of the coding system. Both coders were blind to all participant information, including demographics, asthma medication use, and cytokine responses. Due to the ordinal nature of the data, intercoder agreement was calculated several ways. The intercoder correlation (Pearson r) was .74, which is comparable to previous studies using similar interviews (e.g., Cox & McAdams, 2014). The kappa statistic for agreement on whether a memory demonstrated any perspective-taking (coding 0 vs. 1 or 2) was .61 and the kappa statistic for whether a memory demonstrated minimal or a lot of perspective-taking (coding 0 or 1 vs. 2)

was .79. Disagreements within the 94 memories were resolved by consensus discussion. Codes on each of the two memories were averaged to create an overall perspective-taking code for each parent (scores ranged from 0–2). Examples from interviews at each coding point are displayed in Table 1. The average score of perspective-taking was .21 (*SD*=.37) with 30% of parents demonstrating perspective-taking in one or both memories.

Preliminary validation of the perspective-taking measure within our sample began with the supposition that perspective-taking processes would allow parents to better anticipate the needs and responses of their children, and, in turn, reduce stress and conflict within the family. Supporting the validity of this measure, we found that higher perspective-taking scores were significantly correlated with lower levels of objectively-rated family stress as measured by the Life Stress Interview (Hammen, 1991; r=−.18, p<.05) and with greater engagement with family routines as reflected in higher scores on the Family Routines Inventory (Jensen, James, Boyce, & Harnett, 1983; r=.18, p<.05).

Cytokine Production—Antecubital blood was drawn into BD Cell Preparation Tubes (Becton Dickinson, Franklin Lakes, NJ) containing sodium heparin. Peripheral blood mononuclear cells (PBMCs) were isolated by density-gradient centrifugation according to the manufacturer's instructions and then dispensed into 24-well culture plates in the presence of several different mitogen configurations following procedures similar to those in previous work (Chen et al., 2006; Kang et al., 1997), specifically, a non-specific stimulation to measure Th-1 and Th-2 cytokine production, adaptive immunity stimulation by asthma-relevant ligands, and stimulation of innate immune pathways to measure the production of proinflammatory cytokines. The extent to which glucocorticoids regulate inflammatory signaling (i.e., glucocorticoid sensitivity) was measured by repeating some of the above stimulation protocols in the presence of cortisol.

First, we measured Th-1 versus Th-2 cytokine production following non-specific stimulation by incubating 0.5×10^6 PBMCs with 25 ng/mL of phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich, St. Louis, MO) + 1 ug/mL of ionomycin (INO; Sigma-Aldrich, St. Louis, MO) for 24 hours at 37°C in 5% CO2, similar to previous studies (e.g., Chen, Fisher, Bacharier, & Strunk, 2003; Chen et al., 2006). An unstimulated well with no mitogen but the same number of PBMCs was cultured under the same conditions. Following incubation, supernatants were harvested using centrifugation and frozen at −80°C until assayed in batch via electrochemiluminescence on a SECTOR Imager 2400A (Meso Scale Discovery, MSD). Assays were performed using 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 2.67–4.86%. Cytokine responses were quantified by subtracting values in the unstimulated wells from those in the PMA/INO wells.

Second, we measured Th-1 versus Th-2 cytokine production after incubation with asthma-specific ligands of cockroach and dust mite extract (adaptive immunity). Here, 5×10^6 PBMCs were dispensed into culture wells containing 10 ug/mL of cockroach extract (50:50 mixture of American and German cockroach; Greer, Lenoir, NC) and into wells containing 10 ug/mL of dust mite extract (50:50 mixture of *D. farinae* and *D. pteronyssinus*; Greer,

Lenoir, NC), and incubated for 72 hours at 37°C in 5% CO_2, following protocols used in similar studies (Contreras et al., 2003; Wright et al., 2010). As before, an unstimulated well was included on the plate. Supernatants were assayed in batch using the same MSD platform and reagents as described above, capturing both Th-2 (IL-2, IL-4, IL-5, and IL-13) and Th-1 (IFN-γ, IL-10) cytokine production. Mean inter-assay coefficients of variation were 1.98–4.24%. Values in unstimulated wells were subtracted from values in active wells prior to analysis.

Third, we measured pro-inflammatory cytokine production following stimulation by bacterial and viral analogue ligands by dispensing 0.5×10^6 PBMCs into wells containing . 10ng/mL of lipopolysaccharide (LPS; a molecule found on Gram-negative bacteria that stimulates the Toll-Like Receptor-4 pathway; Invivogen, San Diego, CA), 100ug/mL of Poly I:C (double stranded RNA, which stimulates the Toll-Like Receptor-3 pathway; Invivogen, San Diego, CA), or 10ug/mL oligodeoxynucleotides (ODN; single-stranded DNA, which stimulates the Toll-Like Receptor-9 pathway; Invivogen, San Diego, CA) as well as an unstimulated well. The plate was then incubated for 24 hours at 37°C in 5% CO_2. Supernatants were assayed in batch using the Sector Imager and MSD's Human Pro-Inflammatory Tissue II Culture kit, which included measurement of IL-1β, IL-6, and TNF-α. Interassay coefficients of variation were 3.31–10.27%. As above, unstimulated values were subtracted from stimulated values prior to analysis.

Lastly, glucocorticoid sensitivity was measured by co-incubating 0.5×10^6 PBMCs with either100ug/mL of Poly I:C, and 1.38×10^{-6} M hydrocortisone (Sigma-Aldrich, St. Louis, MO) or 25 ng/mL of PMA, 1 ug/mL INO and 1.38×10^{-6} M hydrocortisone (Sigma-Aldrich, St. Louis, MO) for 24 hours at 37°C in 5% CO2, similar to protocols in previous studies (Miller et al., 2009; Miller & Chen, 2010). An unstimulated well was also included on the plate. Supernatants were assayed in batch using the MSD Human Pro-Inflammatory Tissue II Culture kit to measure IL-1β, IL-6, and TNF-α for Poly I:C+Cortisol and the MSD Th-1/Th-2 kit for PMA/INO+Cortisol. As per above, unstimulated values were subtracted out prior to analysis. Interassay coefficients of variation were 2.78–10.14% At the dose used, cortisol suppresses production of cytokines, so higher values of cytokine production can be interpreted as reflecting greater insensitivity to glucocorticoid inhibitory signals.

Parental Warmth—To test whether associations with parental perspective-taking simply reflected a more general positive relationship between parents and children, youths reported on their perceptions of parental warmth over the past year using a nine-item measure developed by Brody et al (2001). Youths rated the frequency of how often parents acted lovingly or supportively toward them on a 4-point scale (from "never" to "always"), including such items as "During the past 12 months, how often did your parent tell you s/he loves you?" or "During the past 12 months, when you and your parent spent time together, how often did your parent help you with something that was important to you?" The 1-year test–retest correlation on this measure has been reported as $r = .41$ (H. Kim, Ji, & Kao, 2011), and Cronbach's α in our current sample was .91. Scores on this scale have been shown to relate to nurturing caregiving behaviors as well as lower levels of child psychopathology symptoms (Brody et al., 2001; I. J. Kim et al., 2003). However, scores were not correlated with perspective-taking codes in the present sample (r=.00, p=.99).

Depressive Symptoms—To rule out the possibility that depressive symptoms may contribute either to parents' ability to take the perspective of others or to their children's immune responses, depressive symptoms in parents and in children were assessed. Parents completed the 10-item Center for Epidemiological Studies Depression Scale Short Form (CESD; Bjorgvinsson et al. 2013), a widely used depression screen, and youths completed the Anxious/Depressed subscale of the Youth Self Report (YSR; Achenbach & Rescorla, 2001), which assesses the extent to which 13 internalizing behaviors are characteristic of the youth for the past 6 months, including "I feel worthless or inferior" and "I cry a lot." Perspective-taking codes were not significantly correlated with parents' depressive symptoms (r=−.14, p=.109), but were significantly were correlated with children's YSR scores (r=−.19, p=.036), such that children who had parents who engaged in more perspective-taking reported lower levels of internalizing symptoms.

Covariates—Demographic information on youth age, gender, and ethnicity, parent gender and parent's years of education were collected during the laboratory visit and included as covariates in analyses to statistically control for the possibility that inflammatory responses or parental perspective-taking may differ across ages, ethnic and socioeconomic groups, or the gender of the participant. The number of days in the past week in which children took an inhaled corticosteroid and the number of days in which they took a beta-agonist medication were also recorded for each type of medication and included as covariates to account for the possibility that stimulated cytokine responses may be affected by exposure to these types of medication. Additionally, classifications of asthma severity were made using National Asthma Education and Prevention Program/Expert Panel Report 2 guidelines and included as a covariate. These classifications are based on the higher of symptom frequency and medication use, paralleling the approach of previous researchers (Bacharier et al., 2004). Ratings ranged from 1 to 4, where 1= mild intermittent, 2=mild persistent, 3= moderate, and 4=severe asthma.

Statistical Approach

Statistical analyses first assessed descriptive statistics for variables of interest. Next, multiple regressions were used to regress stimulated cytokine responses onto parent perspective-taking scores, controlling for youths' age, ethnicity, gender, parent's gender, parent's years of education, beta-agonist medication usage (number of days in past week), inhaled steroid medication usage (number of days in past week), and asthma severity. After this, multiple regression analyses were re-run to assess alterative explanations of whether associations with spontaneous perspective-taking remained after accounting for 1) a more general positive characteristic of the parent-child relationship (parental warmth) or 2) depressive symptoms in parents and children. Analyses were also re-run to examine alternate coding of perspective-taking, specifically, log-transformation of the perspective-taking variable and binary coding of the perspective-taking variable.

Results

Preliminary Analyses

Descriptive statistics for study variables are presented in Table 2.

As reported in previous research (citation masked), principal components analyses were used to create cytokine composites, resulting in two-factor solutions for PMA/INO, PMA/INO+Cortisol, cockroach, and dust mite stimulations reflecting Th-1 versus Th-2 cytokines. Consequently, cytokine values were standardized and then IL-10 and IFN-γ values were averaged to create Th-1 composites for each ligand and IL-2, Il-4, IL-5, and IL-13 values were averaged to create Th-2 composites.

For assays involving proinflammatory cytokine production from TLR stimulation (and potential regulation by glucocorticoids), single factor solutions emerged. Accordingly, we created composite indicators for each ligand, by standardizing and then averaging values of IL-1β, IL-6, and TNF-α.

Parent Perspective-Taking and Youth Cytokine Production

Multiple regression analyses revealed that children who had parents with higher levels of perspective-taking showed significantly smaller Th-2 (B=−.55, SE=.25; p=.032), but not Th-1 (B=−.43, SE=.27; p=.105), cytokine responses to nonspecific stimulation with PMA/INO.

Regarding asthma-relevant ligands, greater parent perspective-taking was associated with smaller child Th-1 (B=−.55, SE=.21; p=.010) and Th-2 (B=−.63, SE=.23; p=.007) cytokine responses following stimulation with cockroach extract. Parent perspective-taking was also significantly associated with smaller Th-1 (B=−.59, SE=.20; p=.004), and marginally associated with Th-2 (B=−.40, SE=.22; p=.072) cytokine responses following stimulation with dust mite extract. In each case, children with parents who engaged in more perspective-taking showed smaller stimulated cytokine responses in response to asthma-relevant ligands.

With respect to TLR stimulation of proinflammatory cytokine responses, higher parent perspective-taking was associated with smaller proinflammatory cytokine responses to Poly I:C stimulation (B=−.51, SE=.25; p=.045), but was not significantly associated with cytokine responses to LPS (B=−.02, SE=.25; p=.945) or ODN (B=.25, SE=.22; p=.249) stimulation.

For assays of glucocorticoid sensitivity, parent perspective-taking was associated with both Th-1 (B=−.57, SE=.23; p=.017) and Th-2 (B=−.48, SE=.24; p=.047) cytokine responses to stimulation by PMA/INO+ cortisol. In addition, perspective-taking was significantly associated with smaller proinflammatory cytokine responses to Poly I:C+ cortisol stimulation (B=−.87, SE=.24; p=.000). These associations indicate that children who had parents who demonstrated greater perspective-taking showed a greater sensitivity to glucocorticoid inhibitory signaling.

Table 3 presents a summary of multiple regression results.

Alternative Explanations

Specificity of Perspective-Taking—To assess whether associations with parent perspective-taking might be due to more general positive parenting characteristics, analyses were re-run while including parental warmth as an additional covariate in the models. This did not alter the pattern of significant and nonsignificant findings in prior results, suggesting

that associations with perspective-taking are not accounted for by broader positive parent-child relationship characteristics. Analyses were next run while including parental depressive symptoms (measured using the CESD) and youth internalizing symptoms (measured using the YSR). Findings remained largely the same, with the exception that the association of Th-1 cytokine responses to stimulation by PMA/INO strengthened slightly to became marginally significant (B=−.48, SE=.27; p=.074), while the association of proinflammatory cytokines to stimulation by Poly I:C diminished slightly to marginal significance (B=−.45, SE=.25; p=.076).

Alternative Scoring of Perspective-Taking—Because only thirty percent of parents engaged in perspective-taking, the resulting variable showed notable skewness (skewness statistic= 2.03, std error=.12). To ensure that observed associations were not affected by the distribution of responses, all regressions were re-run using a log-transformation of perspective-taking and then secondly, using a binary coding of perspective-taking representing whether or not parents demonstrated any amount of perspective-taking in either of the memories. Similar results were obtained when using a log-transformed version of the perspective-taking code, with the exception that associations with Th-2 cytokine production following stimulation by PMA (B=−1.57, SE=−.85; p=.068) and PMA+ Cort (B=−1.43, SE=.81; p=.082) shifted slightly to marginal significance. When re-running analyses to predict immune outcomes from a dummy code representing whether or not parents engaged in perspective-taking (0=no perspective-taking and 1=any perspective-taking), Th-2 responses to stimulation with dust mite extract became significant (B=−.40, SE=.17; p=.024), whereas Th-1 responses to PMA + Cort (B=−.33, SE=.19; p=.090) and proinflammatory responses to Poly:IC (B=−.36, SE=.20; p=.076) shifted slightly to marginal significance. Th-2 responses to stimulation by PMA (B=−.19, SE=.21; p=.352) and PMA +Cort (B=−.21, SE=.20; p=.294) became non-significant. Figure 1 illustrates the difference in average level of the proinflammatory cytokine composite in response to stimulation by PMA+Cort for children of parents who did or did not demonstrate any evidence of perspective-taking.

Discussion

Using a novel assessment of parental perspective-taking in a clinical sample of children with asthma, the current study found support for the hypothesis that parents who demonstrated higher levels of cognitive empathy would have children with smaller cytokine responses to a variety of ligands using an analogue laboratory paradigm. Specifically, greater spontaneous perspective-taking by parents was related to lower stimulated Th-2 cytokine production in response to non-specific stimulation of PBMCs, and as well, to lower Th-1 and Th-2 cytokine responses to asthma-specific ligand stimulation of PBMCs. Greater parent perspective-taking also was associated with lower proinflammatory cytokine responses in response to stimulation of the TLR pathway with a viral analogue ligand in children with asthma. Finally, greater parental perspective-taking was associated with greater sensitivity of youths' immune cells to the anti-inflammatory effects of glucocorticoids. Results were similar, albeit somewhat attenuated, when using alternative calculations for perspective-taking (e.g., presence/absence). Importantly, these associations could not be better accounted

for by parental warmth, parent or youth depressive symptoms, age, gender, ethnicity, asthma medication use, or asthma severity. Together, these findings suggest that children who have parents who more readily take the perspectives of others may have cells that mount smaller inflammatory responses to allergens that trigger asthmatic responses, as well as may mount smaller proinflammatory responses to viruses that can contribute to asthma morbidity. Moreover, that these children's samples showed greater sensitivity to cortisol in the laboratory paradigm indicates that the administration of synthetic glucocorticoids might have more beneficial effects for asthma control in these children. However, we note that the above implications are speculations about how a laboratory paradigm might translate into real-world asthma responses, but we did not have data on children's responses to asthma triggers in daily life or on children's responsiveness to medications.

Although the current study was unable to assess mechanisms for the observed effects, there are several possible psychosocial explanations for why parental perspective-taking would be related to youths' cytokine production profiles. One possibility is that parents who are higher on dispositional cognitive empathy, and who thus engage spontaneously in perspective-taking, are better able to anticipate and respond to the general needs of their children, facilitating a more harmonious and less stressful home environment, with subsequent effects on stress-responsive physiological systems in children (Chen, Miller, Kobor, & Cole, 2010). More specific to asthma, it is also possible that parental perspective-taking allows parents to more adeptly encourage better asthma management behaviors, such as medication adherence and limiting allergen exposures, that in turn have implications for asthma inflammatory processes. Meta-analytic research examining the effects of social support on medical treatment fidelity is supportive of this possibility (DiMatteo, 2004). These possibilities are further supported by the observed correlations between perspective-taking and measures of chronic family stress and family routines, which have been linked to medication management and asthma morbidity (Schreier & Chen, 2010).

Consistent with previous work (Manczak et al., 2016), the observed associations were not accounted for by youths' ratings of parental warmth or depressive symptoms in either family member, suggesting that there may be something unique to parents' ability and inclination to take the perspectives of others that goes beyond the effects of an emotionally nurturing family environment or more optimal mental health. Conceptually, warmth may be seen as encompassing a wide swath of interpersonal behaviors that convey connectedness, kindness, and positivity, thus perhaps relating to important affective processes within families. In contrast, perspective-taking reflects an underlying tendency to be interested in and understand the mental states of others, perhaps better capturing cognitive features of interpersonal interactions. One possibility is that parental perspective-taking may inform a broader range of behaviors in addition to encouraging warm interactions (Strayer & Roberts, 2004), such as curtailing use of harsh discipline or encouraging more consistent parenting responses. Another possibility is that parents who more naturally consider the perspectives of others may simply be more sensitive to the emotional and physical states of their children (Kochanska, 1997), allowing them to optimize and tailor their responses to the needs of a particular child in ways that are not captured by items assessing general parenting dimensions. Regardless, this suggests that parental perspective-taking is not redundant with

warmth (nor with parent and child mental health), but rather may be an important additional dimension to assess.

The current work is the first to link parents' perspective-taking to a wide range of cytokine responses in children with asthma. It relied on a multi-method assessment of both psychological and biological processes and introduced a novel assessment of spontaneous perspective-taking that overcomes limits of possible bias in self-reporting. However, there are several important limitations to acknowledge. First, the research was cross-sectional, and thus causality as well as directionality are impossible to determine. Another limitation is that only thirty percent of parents spontaneously mentioned the perspectives of others during one of their memory discussions. Future work might consider probing more than two memories to assess perspective-taking. In addition to potential floor effects, the assessment in the current work provides a very conservative index of parental perspective-taking, such that it is only capturing especially cognitively-empathic parents who spontaneously engage in perspective-taking, but over-looks parents who have the capacity to for perspective-taking if prompted. The extent to which spontaneous demonstrations of perspective-taking more closely track actual protective processes in families than trait-like measures of empathy remains to be investigated. It is worth noting, however, that the observed effects are consistent with previous work using a self-report measure of empathy, which had greater variability in responses and was found to be negatively associated with circulating CRP levels in healthy children (Manczak et al., 2016). Furthermore, an advantage of this interview approach is that by not specifically prompting for aspects of empathic consideration, responses can be interpreted as reflecting dominant values and motivations as they naturally occur in the lives of participants (McAdams, Hoffman, & Day, 1996), which overcomes concerns about self-presentation in responding. Likewise, the topic of the interview did not specify that the parent discuss aspects of their relationship with their participating child. Thus, it is impossible to know whether any perspective-taking that was observed is reflective of parental cognitive empathy as it occurs with regard to that child. However, if empathy is conceptualized as a dispositional trait, it is presumed that expressions of perspective-taking would be largely stable across close relationships. In addition, we were unable to consider differences in parental perspective-taking for mothers versus fathers. Intriguingly, zero-order correlations suggest that fathers had higher levels of perspective-taking than mothers. This may be a function of the fact that—consistent with trends in developmental research—fewer fathers participated in the current research than mothers and thus, those who did may be unusually connected with their children. Further research is necessary to examine this possibility.

There are also several limitations related to the stimulated cytokine paradigms and medication assessment. Although analogue culture paradigms are frequently used in studies of asthma responsiveness (e.g., Chen et al., 2006; Kang et al., 1997, Waage & Bakke, 1988), formal validation studies have not been done. It is therefore unclear to what extent our findings translate into real-life asthma responses to triggers in children, though we caution that this would be challenging to determine (given the inherent differences in trigger exposures, allergic status, medications prescribed, and medications taken across patients with asthma). In addition, significant associations did not emerge for stimulation by several ligands, such as LPS or ODN. However, given the complex, specialized processes and

counter-regulatory mechanisms involved in cytokine production, it is not unusual or surprising for associations to differ across biological outcomes (e.g., Sesso et al., 2007). We also did not account for different cell types within peripheral blood mononuclear cells. Lastly, research in clinical populations often necessitates working with samples made up of individuals who differ among a number of factors related to disease outcomes, including symptoms severity, medication dosage, medication usage, or health care access, for example. Although we attempted to statistically adjust for these factors as much as possible, it is difficult to isolate whether a variable is exerting a causal effect in these sorts of clinical studies. Nonetheless, these observational studies still provide important information into psychosocial factors related to clinical processes.

Despite these limitations, the results of the current study raise several important questions for future research. For example, what are the mechanisms of the observed associations? Behaviorally, might diary or observational assessments identify aspects of parent-child interactions in the daily lives of families that are unique to more empathic parents, such as coaching healthy coping skills or greater use of validation and reflective listening? Biologically, more work on the cascade of processes that may give rise to these differences in stimulated cytokine production will be important. Here, examining additional levels of analysis, such as differences in gene expression or hormone secretion relating to parental perspective-taking may hold promise in elucidating mechanisms. Examining associations within different pediatric inflammatory disease models, such as inflammatory bowel disorder, should also be considered.

Regardless of these unanswered questions, the present work adds to research on the importance of early family relationships for youths' physical health, identifying multiple asthma-relevant inflammatory markers that relate to parents' spontaneous expressions of perspective-taking within a population of children with a chronic illness. Together, this work supports the possibility that parental empathy may facilitate important physical health processes in children.

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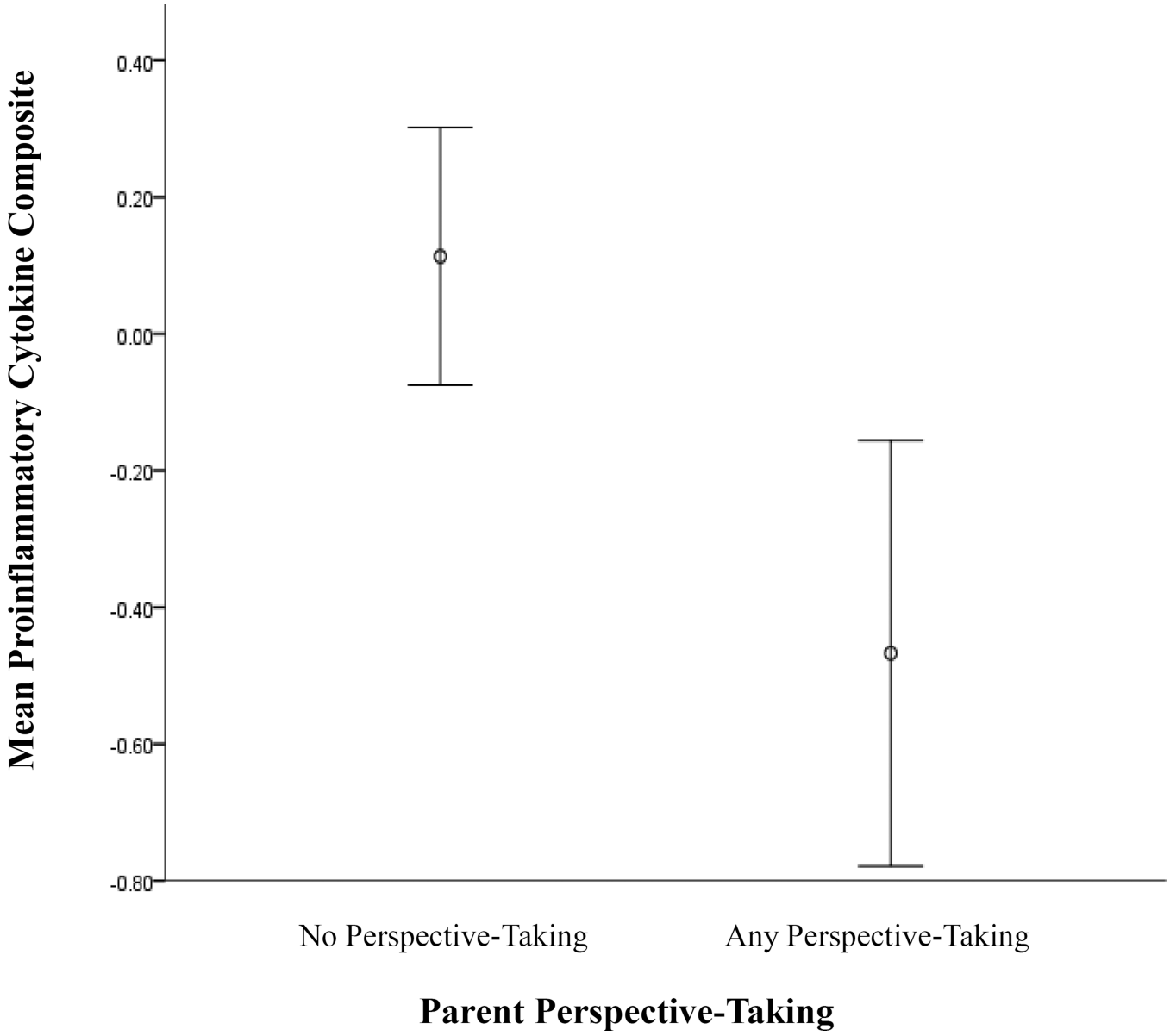

Figure 1.

Mean Proinflammatory Cytokine Production in Response to Stimulation by Poly I:C + Cortisol For Children of Parents Who Did and Did Not Demonstrate Perspective-Taking.

Note. The Proinflammatory Cytokine Composite reflects sum of standardized values of IL-1β, IL-6, and TNF-α in response to stimulation by Poly I:C in the presence of cortisol.

Table 1

Life Story Challenge Prompts and Coding Examples

Interview prompt for family-related memory	I'd like to hear about a challenge or struggle you've experienced in your family. We're interested in hearing about any scene that you remember clearly in which you and your family experienced or went through a problem or struggle. Please tell me about what happened in the scene, and what you were thinking and feeling. I'm also interested in hearing about how you dealt with this challenge, any things you felt you learned from it, and any ways in which this challenge affected your outlook on life. Why does this particular scene stand out as important? What do you think it says about who *you* are as a person? What do you think it says about your family?
Interview prompt for self-related memory	Second, I'd like to hear about a challenge or struggle you – yourself -- have experienced in your own life. Pick a scene from any point in your adult life. As before, please tell me what happened, and what you were thinking and feeling. You can also tell me about how you dealt with this challenge, any things you felt you learned from it, and any ways in which this challenge affected your outlook on life. Why does this particular scene stand out as important? What do you think it may say about who you are as a person?
Example from an from interview that received a code of "2"	[Describing death of neighbor's child]: Everyone was very sad. I think it was very hard for my girls to see a child die like that. I think …the funerals we go to tend to be for someone of a grandparent, a senior's age, and it was sort of a stunning thing for them to go to a child['s]. And so, I think it stretched everybody in some ways.
Example from an interview that received a code of "1"	[Describing adoption process]: I think realizing… [adoption is] a really tenuous process and just everything that goes with it. From the grief on both sides, the grief of the birth parents, the grief of the child growing up…
Example from an interview that received a code of "0"	[Describing finding daughter after suicide attempt]: I knew that rationally, like, this [method] never would've hurt, never would've hurt her, but just so it was more of just… 'I've got to deal with this.' I was just calm. I just [helped] her and just said okay, come downstairs.

Note. Identifying details from interviews have been removed or modified to protect confidentiality.

Table 2

Descriptive Statistics and Intercorrelations for Demographic and Psychosocial Variables

	Mean	SD	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. Child Age	14.00	2.08	.25*	−.12	.10	.09	−.02	.15	.14	−.11	−.08	−.24*	.05	.11
2. Parent Age	45.55	6.22		.03	.07	−.13	−.09	.02	.35*	−.05	−.04	.00	−.07	.25*
3. Parent Years Education	16.19	2.73			.03	−.20*	−.12	.02	.31	−.15	.08	.24*	−.32*	.01
4. Days Inhaled Corticosteroid	2.39	3.01				.12	.26*	.00	.08	−.06	.09	−.02	−.11	.02
5. Days Beta Agonist	1.41	2.01					.26*	.12	−.09	−.02	.16	−.04	−.01	−.06
6. Asthma Severity	2.38	.98						.10	−.16	.05	.02	−.08	.07	−.02
7. Child Gender (Female)	42%								.09	.04	−.10	−.04	.09	.27*
8. Child Ethnicity (Caucasian)	62%									.10	−.09	−.05	−.25*	.03
9. Parent Gender (Female)	88%										−.20	.05	.16	−.01
10. Perspective-Taking	.21	.37										.00	−.14	−.19*
11. Parental Warmth	29.05	5.52											−.22*	−.27*
12. CESD	6.16	4.47												.17
13. YSR	6.90	5.12												

Note. Days Beta Agonist and Days Inhaled Corticosteroid refer to the number of days in the past week that participants used either form of medication. Asthma Severity= National Asthma Education and Prevention Program/Expert Panel Report 2 guidelines. Child gender and parent gender were dummy coded where 1= female and 0=male. Child ethnicity was dummy coded where 1=Caucasian and 0=Non-Caucasian. Percentage values indicate the percentage of the sample that was female or Caucasian. CESD= Center for Epidemiological Studies Depression Scale (parent report). YSR = Anxious/Depressed Subscale of Youth Self-Report (youth report).

Table 3

Summary of Associations between Parent Perspective-Taking and Youth Cytokine Production Outcomes

	B	*SE*	*p*	sr^2
Nonspecific Stimulation				
PMA/INO: Th-1	−.43	.27	.105	.02
PMA/INO: Th-2	−.55	.25	.032	.04
Adaptive Immune Stimulation				
CR: Th-1	−.55	.21	.010	.05
CR: Th-2	−.63	.23	.007	.05
DM: Th-1	−.59	.20	.004	.06
DM: Th-2	−.40	.22	.072	.02
Innate Immune Stimulation				
Poly I:C: proinflammatory	−.51	.25	.045	.03
LPS: proinflammatory	−.02	.25	.945	.00
ODN: proinflammatory	.25	.22	.249	.01
Glucocorticoid Sensitivity				
PMA/INO+Cortisol: Th-1	−.57	.23	.017	.05
PMA/INO+Cortisol: Th-2	−.48	.24	.047	.03
Poly I:C+Cortisol: proinflammatory	−.87	.24	.000	.11

Note. sr^2= semi-partial r squared; PMA/ION= phorbol 12-myristate 13-acetate + ionomycin; Th-1 = T helper 1 cytokine composite (IFN- γ & IL-10); Th-2 = T helper 2 cytokine composite (IL-2, Il-4, IL-5, and IL-13); CR= Cockroach; DM= Dust mite; Proinflammatory= Proinflammatory cytokine composite (IL-1β, IL-6, & TNF-α); LPS= lipopolysaccharide; ODN= oligodeoxynucleotides. Standardized beta weights are presented for perspective-taking in models that also statistically controlled for youth age, gender, ethnicity, parent gender, parent education, number of days in past week using beta agonists, number of days in past week using inhaled corticosteroids, and asthma severity.