Development and Psychopathology (2022), **34**, 587–596
doi:10.1017/S0954579421001577

CAMBRIDGE UNIVERSITY PRESS

Special Issue Article

Harshness and unpredictability: Childhood environmental links with immune and asthma outcomes

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Abstract

The environment has pervasive impacts on human development, and two key environmental conditions – harshness and unpredictability – are proposed to be instrumental in tuning development. This study examined (1) how harsh and unpredictable environments related to immune and clinical outcomes in the context of childhood asthma, and (2) whether there were independent associations of harshness and unpredictability with these outcomes. Participants were 290 youth physician-diagnosed with asthma. Harshness was assessed with youth-reported exposure to violence and neighborhood-level murder rate. Unpredictability was assessed with parent reports of family structural changes. Youth also completed measures of asthma control as well as asthma quality of life and provided blood samples to assess immune profiles, including in vitro cytokine responses to challenge and sensitivity to inhibitory signals from glucocorticoids. Results indicated that harshness was associated with more pronounced pro-inflammatory cytokine production following challenge and less sensitivity to the inhibitory properties of glucocorticoids. Furthermore, youth exposed to harsher environments reported less asthma control and poorer quality of life. All associations with harshness persisted when controlling for unpredictability. No associations between unpredictability and outcomes were found. These findings suggest that relative to unpredictability, harshness may be a more consistent correlate of asthma-relevant immune and clinical outcomes.

Keywords: asthma; harshness; inflammation; unpredictability

(Received 27 July 2021; revised 15 November 2021; accepted 16 November 2021; First Published online 20 December 2021)

The environment profoundly shapes the way humans develop. Humans adopt behavioral and biological strategies for coping with positive and negative aspects of their environments. In turn, these strategies have implications for developmental processes and consequently health. The present study seeks to examine the relationship between two adverse environmental conditions – harshness and unpredictability – and youth's biological processes and health in the chronic disease context of asthma.

Environmental harshness and unpredictability

Certain environmental conditions are key in tuning development, and one theoretical model specified by Ellis et al. (2009) has highlighted harshness and unpredictability as two conditions that can have pervasive impacts on childhood development. In this model, harshness refers to environmental factors that can increase the rate of morbidity or death in a population. These can include socioeconomic disadvantage, harsh or neglectful parenting, neighborhood deprivation, and exposure to violence in modern Western societies. A second environmental condition, unpredictability, refers to random variations in external factors important to development for which occurrence is uncertain over time or over space. Examples in modern Western societies include changes in parental figures, residential location, and parental employment. Harshness and unpredictability are thought to be conceptually distinct environmental conditions – harsh environments can vary in predictability (e.g., exposure to maltreatment can be stable or erratic across time) and unpredictable environments can vary in harshness (e.g., family composition may change frequently but the level of harshness within the household may be maintained).

From an evolutionary perspective, harshness and unpredictability are theorized to impact childhood development through shaping of resource-allocation tradeoffs (Ellis et al., 2009). Given that resources are limited, tradeoffs involve organisms prioritizing investment in one domain at the expense of other domains. For example, the immune system protects the body from invading pathogens, but such defense is metabolically costly to maintain and to mount (McDade, 2005) and further comes at the expense of investment in musculoskeletal growth (Rauw, 2012). Patterns of tradeoffs prioritizing behaviors and biological processes that increase the likelihood of passing down one's genes, over time, result in life history strategies that are fitting for the organism's environment. These strategies are postulated to vary on a slow-fast continuum (Ellis et al., 2009): fast strategies are characterized by earlier reproductive behaviors and development, having more offspring, and less stable relationship bonds, whereas slower strategies are characterized by delayed reproductive development in order to

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Cite this article: Lam, P. H., *et al.* (2022). Harshness and unpredictability: Childhood environmental links with immune and asthma outcomes. *Development and Psychopathology* **34**: 587–596, https://doi.org/10.1017/S0954579421001577

allocate resources to growing, having more stable relationship bonds, and having fewer offspring.

Individual differences in life history strategies along the fast-slow continuum are evident, and these differences are postulated to be driven in part by environmental conditions. Specifically, conditions entailing more harshness and more unpredictability are thought to facilitate the development of faster life history strategies in organisms (Ellis et al., 2009). In the case of harshness, exposure to environmental factors that suggest short life expectancies should favor allocating resources toward faster life history strategies to maximize the chances of reproduction before death. In the case of unpredictability, uncertainty in the future would bias against long-term investments and thus also favors faster life history strategies. Furthermore, as harshness and unpredictability are conceptually distinct dimensions, they are also thought to have independent associations with faster life history strategies. In sum, harshness and unpredictability are two key environmental conditions theorized to independently shape childhood development through favoring faster life history strategies.

Empirical evidence for harshness and unpredictability

Empirical research supports the proposition that harshness and unpredictability are associated with faster life history strategies. For example, adolescents who experienced more harshness, as operationalized by exposure to violence, was less sexually restricted (Brumbach et al., 2009). Similarly, a meta-analysis has demonstrated that childhood maltreatment, an example of environmental harshness, was associated with earlier sexual debut and having multiple sexual partners in adolescence and adulthood (Wang et al., 2019). Ecological harshness has also been linked to faster life history strategies, such that younger women residing in neighborhoods with lower life expectancy gave birth at an earlier age (Wilson & Daly, 1997). Furthermore, threat, a related adversity dimension characterized by direct harm or threat of harm (but excludes ecological variables such as neighborhood-level violence; McLaughlin et al., 2014), has also been linked to faster life history strategies. Specifically, a meta-analysis demonstrated that threat, as operationalized by physical and emotional abuse, sexual assault, and victimization, was associated with indicators of faster life history strategies, including earlier pubertal timing and accelerated cellular aging (Colich et al., 2020). Unpredictability has similarly been associated with faster life history strategies. For example, in two longitudinal samples, exposure to childhood unpredictability, as operationalized by changes in parents' employment status, cohabitation status, and residence, was associated with indicators of faster life history strategies, including more short-term sexual partners in adolescence (Belsky et al., 2012) and in adulthood (Simpson et al., 2012; Szepsenwol et al., 2017). As such, extant research supports the notion that harshness and unpredictability are associated with fast life history strategies.

An additional hypothesis from the model by Ellis et al. (2009) is that harshness and unpredictability should have independent effects on life history strategies. There is less empirical evidence to support this proposition, but some nascent findings have emerged. In a longitudinal study, harshness (operationalized by income-to-needs ratio) and unpredictability (operationalized by paternal transitions, household moves, and parents' employment changes) were repeatedly assessed across the first 5 years of children's lives (Belsky et al., 2012). Greater childhood unpredictability was prospectively associated with greater number of sexual partners during adolescence, above and beyond the effects of harshness. Childhood harshness was found to be *indirectly* associated with greater number of sexual partners in adolescence via lower maternal sensitivity in childhood, and this indirect pathway persisted above and beyond the effects of unpredictability (Belsky et al., 2012). Other studies have found that harshness and unpredictability are distinct in being associated with different indicators of life strategies at different developmental stages. For example, in another longitudinal study, harshness (operationalized by exposure to violence) was independently associated with less sexual restrictedness in *adolescence*, whereas unpredictability (operationalized as inconsistency in childhood environments) was independently associated with a composite measure of faster life strategies in *young adulthood* (a composite representing less sexual restrictedness, less effort in maintaining somatic health, and higher social deviance; Brumbach et al., 2009). As such, there are nascent findings that suggest harshness and unpredictability may have independent effects on life history strategies, but this proposition has yet to be well-established empirically.

Extension of the Ellis et al. (2009) model to the immune system

The model by Ellis et al. (2009) has largely focused on linking environmental conditions to interpersonal and reproductive outcomes, with relatively less research considering the implications of these conditions for other biological processes. One body system that is thought to be sensitive to environmental tuning is the immune system (Miller et al., 2011). When injuries or infections are detected, the immune system mounts an acute inflammatory response that primarily involves innate immune cells – namely, neutrophils, monocytes, dendritic cells, and macrophages. Specifically, innate immune cells accumulate at the site of infection and secrete pro-inflammatory cytokines, such as Interleukin (IL)-6, IL-1ß, and tumor necrosis factor (TNF)-α. These pro-inflammatory cytokines recruit other cells to the site, and signal those cells to divide, mature, and release antimicrobial substances. These processes help clear the infection and/or heal the wound. Once that is underway, the HPA axis releases glucocorticoids, which slow down these inflammatory processes and shift cellular behavior towards repair and growth.

This innate inflammatory response is critical for the survival, particularly for invertebrates which are only equipped with innate (but not adaptive) immune systems. As ancestral ecologies involved predation, conflicts, and other events that posed threats to survival and reproduction, it is possible that selective pressures kept this system activated or primed to respond more rapidly following a challenge (Benschop et al., 1996; Dhabhar et al., 1995; Miller et al., 2011). In such environments, an activated tendency would presumably confer a survival advantage to the organism by shortening the interval from an infection or injury to its resolution. Consistent with this hypothesis, pro-inflammatory alleles of inflammation-related genes are more prevalent in populations whose long-term ancestry is characterized by higher (as opposed to lower) burden of infectious diseases (Le Souëf et al., 2000). In addition, possessing a pro-inflammatory tendency may also behaviorally prepare organisms for adverse environments. For example, cellular pro-inflammatory tendencies predicted decision-making that was impulsive, present-focused, and prone to immediate gratification (Gassen et al., 2019). This decision-making profile is consistent with life history theory as behaving in ways that emphasize immediate rewards may yield higher returns in adverse or unpredictable environments where the future is uncertain. In sum, these

https://doi.org/10.1017/S0954579421001577 Published online by Cambridge University Press

findings suggest that the tendency for heightened immune preparedness may have been conserved across evolutionary time.

If so, we would expect that in modern days, adverse environments characterized by harshness or unpredictability would similarly signal cells of the innate immune system to enter a state of heightened preparedness. In their model of chronic early life stress, Miller et al. (2011) describe how a pro-inflammatory state could manifest in cells known as monocytes and macrophages. Specifically, the model proposes a stress-evoked pro-inflammatory phenotype, where these cells (1) mount more exaggerated inflammatory responses to challenges and (2) are less sensitive to inhibitory signals, such as the release of glucocorticoids, that typically are used to terminate inflammatory responses when they are no longer needed. These cellular tendencies result in aggressive and prolonged inflammatory responses. Under adverse environmental conditions where threats are present, such response tendencies might be advantageous because they should help eradicate pathogens more efficiently. However, heightened and unregulated inflammatory responses can, over long periods of time, damage tissues and organs by sustaining a low-grade inflammation in the body (Nathan & Ding, 2010), increasing risks for diseases of aging like diabetes, heart attacks, and stroke (Danesh et al., 2000, 2008; Pearson et al., 2003). As such, adverse environmental conditions may signal the body to express a pro-inflammatory phenotype, which better equips it for survival and reproduction in the short term. However, for modern humans who live many decades, this phenotype may entail a long-term tradeoff of promoting processes that increase the risk of diseases related to aging.

To empirically test whether adverse environments calibrate how innate immune cells operate, studies have used in vitro paradigms that model inflammation in vitro (i.e., outside of the body in small plastic dishes). In these studies, monocytes are exposed to microbial stimuli, such as the bacterial product lipopolysaccharide (LPS). This simulates an infectious challenge for the monocytes, which respond by producing a variety of pro-inflammatory cytokines as described above. One can measure the amount of inflammatory cytokine that is produced and use it as an indicator of the magnitude of the inflammatory response. In a second in vitro paradigm, cells can be simultaneously exposed to a microbial stimulus and a compound that exerts antiinflammatory effects, such as glucocorticoids. In this paradigm, glucocorticoids will partially inhibit the production of cytokines by cells exposed to the microbial stimulus. However, the magnitude of this inhibition varies from person to person. By subsequently measuring cytokines produced under these conditions, researchers can approximate individual's sensitivity to inhibitory agents, or in other words, how effectively their cells respond to "stop" signals.

Using these methods, a handful of studies have examined whether exposure to harshness in childhood would be associated with a pro-inflammatory phenotype. For example, studies have found that children exposed to more environmental harshness, such as socioeconomic disadvantage and harsh family climate, were more likely to have monocytes that displayed larger pro-inflammatory cytokine responses following stimulation (suggesting mounting of more aggressive inflammatory responses) and cells that had lower sensitivity to glucocorticoid inhibition of cytokine production (suggesting lower capacity in ending the inflammatory response; Chen et al., 2006; Ehrlich et al., 2016; Miller & Chen, 2010). Furthermore, in one study, unpredictability (as operationalized by low level of family routines) was associated with greater increases in stimulated production of cytokine over the course of 1.5 years (Schreier & Chen, 2010). To our knowledge, no studies have examined the relationship between unpredictability and immune cell's sensitivity to inhibition signals that regulate inflammatory processes. To sum, existing literature has provided some initial support that harshness and unpredictability may be associated with pro-inflammatory tendencies. However, research has yet to conceptualize work within the Ellis et al. (2009) framework and thus has yet to examine the independent contributions of harshness and unpredictability within the same study.

Examining harshness and unpredictability in a disease framework

In this study, we use childhood asthma as a disease framework that may illustrate the links from environmental conditions – harshness and unpredictability – to hypothesized immune processes and resulting disease outcomes. Asthma is a respiratory disease characterized by inflammation and obstruction of airways, and multiple classes of immune cells play key roles in these processes. When exposed to allergens, pollutants, or infections, immune cells mount a response in the airways that eventuates in mucus production, airway constriction, and shortness of breath. In general, as described above, cells of the innate immune system carry out the first phase of the body's inflammatory responses. However, innate immune cells are not always successful at eliminating the triggering stimulus. At this point, cells of the adaptive immune system get involved. Compared to innate cells, adaptive cells are slower to respond but more effective at targeting specific pathogens. Cells from this adaptive arm of the immune system, mainly T and B lymphocytes, are proximal drivers of airway inflammation in asthma. Immunologists often distinguish between Type 1 (T1) and Type 2 (T2) adaptive immune responses (Barnes, 2001; Spellberg & Edwards, 2001). Both responses are coordinated by T-helper cells, but they involve distinct repertoires of cytokine release and downstream events, which are optimized to neutralize different threats. T1 adaptive responses utilize cytokines such as interferon (IFN)-γ to mobilize T-cell-mediated responses against intracellular pathogens like viruses. By contrast, T2 adaptive responses use the cytokines IL-4, IL-5, and IL-13, to mobilize antibody-mediated responses against extracellular pathogens, like parasites and bacteria. Both T1 and T2 responses are dysregulated in asthma. However, the T2 response is conventionally thought to be most proximally involved in promoting asthma symptoms (Barnes, 2001). For example, T2 cytokines like IL-4 and IL-13 facilitate the release of immunoglobulin E molecules which dock on mast cells in the airways, causing them to facilitate airway constriction and mucus production. Further, the T2 cytokine IL-5 recruits eosinophils to the airways and induces them to release mediators that contribute to chronic inflammation in asthma (Brusselle et al., 2013). In sum, adaptive immune responses play crucial roles in engendering and maintaining asthma symptoms.

Although much asthma research has focused on adaptive immune processes, emerging evidence suggests that innate immune processes also play important roles in facilitating asthma symptoms (Finn & Bigby, 2009). Innate immune cells can recognize pathogens, allergens, and pollutants, and help to trigger the release of cytokines that recruit adaptive immune cells (T- and B-cells) to the site of the threat. That is, innate immune cells can "present" a microbial threat to T-helper cells for identification and can help shift the adaptive immune system's response towards T1 versus T2 and modulate its intensity. For these reasons, the nature and magnitude of the innate response is increasingly

https://doi.org/10.1017/S0954579421001577 Published online by Cambridge University Press

thought to have implications for asthma control (Finn & Bigby, 2009; Suarez et al., 2008; Yang et al., 2006).

Evolutionary theories concerning environmental tuning of the immune system have primarily focused on innate immune responses, rather than adaptive immune responses (Benschop et al., 1996; Dhabhar et al., 1995; Miller et al., 2011). However, threats that trigger innate responses, such as the bacterial product LPS, also elicit downstream production of the T1 and T2 cytokines that are part of the adaptive immune system (Iwasaki & Medzhitov, 2004). In addition, both asthma-relevant immune processes as well as asthma clinical outcomes appear to be sensitive to environmental factors, including harshness and unpredictability. For example, indicators of harshness, including socioeconomic disadvantage and harsh family environments, have been linked to higher in vitro production of T2 cytokines among children with asthma (Chen et al., 2007, 2017; Klinnert et al., 2001). In addition, unpredictability, in terms of household chaos, has been associated with worse asthma control (Weinstein et al., 2019). The present study is novel in investigating both innate and adaptive immune responses to both environmental harshness and unpredictability, as well as their independent contributions to asthma inflammation and clinical outcomes.

The present study

Ellis et al. (2009) proposed harshness and unpredictability as two childhood environmental conditions that can impact development through their links with faster life history strategies. The present study extended this theoretical model to the health domain by assessing how these specific childhood environmental factors relate to immune processes and disease outcomes in the context of asthma. Specifically, this study aimed to examine (1) how childhood exposure to harshness and unpredictability relate to immune responses to challenge and clinical asthma outcomes, and (2) whether there are independent contributions of harshness and unpredictability to these outcomes.

We utilized an in vitro model to gauge the magnitude of both innate and adaptive immune responses to challenge. First, we assessed (a) innate immune responses by quantifying production of innate pro-inflammatory cytokines following stimulation with the bacterial product LPS, and (b) adaptive immune responses by quantifying production of T1 and T2 cytokines following treatment with a cocktail of activating agents. Second, we assessed how sensitive innate and adaptive immune responses are to inhibitory signals from glucocorticoids. We hypothesized that harshness and unpredictability would each be associated with stronger immune responses, characterized by larger stimulated production of innate as well as adaptive (T1 and T2) cytokines, and lower sensitivity to the inhibitory signals from glucocorticoids, as well as worse clinical asthma outcomes, characterized by worse asthma control and worse asthma-related quality of life. In addition, we also hypothesized that these associations would emerge independent of each other.

Method

Participants

Participants were 290 youths, aged 8–17 years ($M = 12.99$, $SD = 2.50$), who had been physician-diagnosed with asthma. Youths were recruited to be part of a larger research project aimed to investigate the neighborhood, family, and individual contributors to asthma disparities. Youths were recruited from the greater Chicago area and outlying suburbs through one health care system, NorthShore University HealthSystem, and one federally-qualified health center, Erie Family Health Center. Families were fluent in English, youths had no current or history of any chronic physical illnesses (except for asthma), had no acute respiratory illness and were not on oral steroids at the time of visit. Youth visited the research lab with a parent (88% mothers) and completed all assessments in a single visit. Youths gave written assent, and parents provided written consent. This study was approved by Northwestern, NorthShore, and Erie Institutional Review Boards.

Measures

Harshness

Harshness was assessed using two measures: youth self-reported exposure to violence and neighborhood-level murder rates. Youth completed the Exposure to Violence Scale (Thomson et al., 2002), a seven-item questionnaire that assesses lifetime exposure to direct victimization (e.g., *Have you ever been attacked with a knife or other sharp object?*), witnessing violence (e.g., *Have you ever seen or been present when someone was shot?*), and victimization of friends or family members (e.g., *Have any of your friends been hurt or killed by a violent act?*). Each of the seven probes was a binary query (yes vs. no) about a different type of violence exposure. Because this was not a frequency measure and because the distribution was skewed, a binary variable was computed to reflect whether youth had experienced at least one of the above events (46% exposed to violence).

To assess neighborhood-level exposure to violence, youth's home addresses were geocoded using ArcGIS Pro (ESRI, 2018) and linked to FIPS codes designating U.S. Census block groups, which are the smallest geographical units for which the Census Bureau publicly reports information and represent between 600 and 3,000 individuals. Each block group was linked to neighborhood murder rates, based on the Uniform Crime Reports from 2010 to 2014 that local police departments provide to the Federal Bureau of Investigation.

A violence exposure composite was then created by averaging the standardized self-reported and neighborhood-level violence measures ($r = .18$) as a proxy for harshness experiences.

Unpredictability

Unpredictability in the family environment was assessed changes to family structure. Specifically, parents were interviewed about the family's household structure throughout their child's lifetime (e.g., *living with two biological parents, living with one biological parent, living with two foster parents*). This information was obtained for each year since their child's birth. Number of times the family's structure had changed throughout the youth's life was categorized as never changed ($n = 218$), changed once ($n = 50$), or changed twice or more ($n = 43$).

Immune measures

Antecubital blood was collected into BD Cell Preparation Tubes (Becton Dickinson, Franklin Lakes, NJ, USA) containing sodium heparin, and peripheral blood mononuclear cells (PBMCs) were then isolated to assess two features of the immune process: stimulated cytokine production (how large immune cells' cytokine responses were to in vitro challenges) and glucocorticoid sensitivity (how sensitive cells were to inhibitory signals that typically regulate this process).

https://doi.org/10.1017/S0954579421001577 Published online by Cambridge University Press

Stimulated cytokine production. PBMCs (400 μl of 1.25×10^6 per ml) were dispensed into wells with (a) 0.1 ng/ml of LPS, a common bacterial product known to generate innate pro-inflammatory cytokine production by monocytes, and (b) 25 ng/ml of phorbol 12-myristate 13-acetate and 1 μg/ml of ionomycin (PMAi), a cocktail that activates lymphocytes to release adaptive T1 and T2 cytokines. The plate also included a negative control well, where PBMCs were incubated with RPMI-1640 media without LPS or PMAi, to measure background cytokine release. After a 24 hr incubation at 37 °C in 5% CO_2, supernatants were harvested and assayed in duplicate via electrochemiluminescence on a Sector Imager 2400A (Meso Scale Discovery, Rockville, MD, USA). This instrument gives accurate, sensitive multiplex readouts across a wide range (Chowdhury et al., 2009).

Innate cytokines. LPS-stimulated wells were assayed for innate pro-inflammatory cytokines IL-6, IL-1β, and TNF-α (average intraassay cv's ranged from 2.92% to 5.32%). A composite of innate pro-inflammatory cytokines was created (α = .92) by averaging the standardized values of each cytokine after background production of cytokines, as measured in the negative control well, had been subtracted out (Chen et al., 2019; Ehrlich et al., 2018).

Adaptive cytokines. PMAi-stimulated wells were assayed for adaptive T1 cytokines IL-2 and IFN-γ (average intraassay cv's were 1.97% and 2.73%, respectively) and for adaptive T2 cytokines IL-4, IL-5, IL-10, and IL-13 (average intraassay cv's ranged from 2.65% to 3.12%). Composites of T1 ($r = .69$) and T2 (α = .94) cytokines were created after adjusting for background production of these molecules as described above.

Glucocorticoid sensitivity. A similar protocol as above was used, but this time incubating PBMCs and LPS/PMAi with 5×10^{-7} g/ml hydrocortisone, which is known to partially inhibit production of the target cytokines at this dose. Subsequent cytokine production is quantified to assess how much this production was suppressed by hydrocortisone as a proxy measure of sensitivity to glucocorticoid's inhibitory signals.

Innate cytokines. Production of the same panels of innate pro-inflammatory cytokines mentioned above were then quantified (average intraassay cv's ranged from 2.73% to 7.10%). To account for individual differences in stimulated cytokine production, the value of each stimulated cytokine (e.g., IL-6 production from the LPS well) was residualized from the corresponding cytokine production value with cortisol inhibition (e.g., IL-6 production from the well with both LPS and hydrocortisone). These residuals were then inversed such that higher values reflect *greater sensitivity to glucocorticoid inhibition*. Finally, a composite was created by averaging the standardized values of the inversed residuals (α = .94).

Adaptive cytokines. Production of adaptive T1 cytokines (average intraassay cv's were 2.04% and 2.94%) and adaptive T2 cytokines (average intraassay cv's ranged from 2.91% to 4.14%) were quantified. Again, residuals were computed to adjust for stimulated cytokine production, which were then inversed such that higher values reflect greater sensitivity to glucocorticoid inhibition. Composites by type of cytokine – T1 ($r = .63$) and T2 (α = .85) – were created by averaging the standardized values of the inversed residuals.

Asthma outcomes

Youth completed measures of asthma control and asthma quality of life. The Asthma Control Test™ is a five-item questionnaire that assesses asthma symptoms (e.g., *How often have you had shortness of breath*), use of rescue medications (e.g., *How often have you used your rescue inhaler or nebulizer medication*), and the effects of asthma on daily functioning (e.g., *How much of the time did your asthma keep you from getting as much done at work, school, or at home*) over the past 4 weeks on a 5-point scale (Nathan et al., 2004). A sum score was created with higher scores indicating better controlled asthma (α = .75, $M = 19.52$, $SD = 3.53$).

Youth also completed the Pediatric Asthma Quality of Life Questionnaire (Juniper et al., 1996), a 23-item measure that gauges asthma symptoms (e.g., *How often during the last week did you have difficulty taking a deep breath*), activity limitations (e.g., *How bothered have you been by your asthma while doing the activity you listed*), and emotional functioning (e.g., *How often during the last week did you feel angry because of your asthma*) on a 7-point scale. A mean score was created with higher scores indicating better asthma quality of life (α = .94, $M = 5.02$, $SD = 1.11$).

Covariates

Demographic variables and medical variables were assessed as covariates. Demographic variables included youth age, sex (male vs. female), and race/ethnicity (White vs. non-White). Medical covariates included asthma severity and use of medications. Asthma severity was determined through a combination of symptoms and medications, ranged from 1 (mild intermittent) to 4 (severe), as recommended by the National Asthma Education and Prevention Program/Expert Panel Report 2 guidelines (Bacharier et al., 2004; $M = 2.40$, $SD = 0.92$). Use of medications referred to number of times inhaled corticosteroids ($M = 1.46$, $SD = 2.11$) and beta agonists ($M = 2.46$, $SD = 3.04$) were used in the past week.

Statistical Analyses

First, we tested whether harshness and unpredictability were associated with immune outcomes (stimulated cytokine production and glucocorticoid sensitivity) and asthma outcomes (asthma control and quality of life) in separate regression models. Next, we tested whether there were independent associations with immune and asthma outcomes when both harshness and unpredictability were entered simultaneously as predictors. All analyses accounted for demographic (age, sex, race/ethnicity) and medical covariates (asthma severity, medication use). Sex and race/ethnicity were effect-coded with male and white being references (coded as −0.5), respectively. In addition, for models that included harshness as a predictor, cluster-robust standard errors were computed to account for dependencies by FIPS codes due to inclusion of neighborhood-level data (White, 1980). Analyses were conducted in R Studio (RStudio Team, 2018) using packages "multiwayvcov" (Graham et al., 2016) and "sandwich" (Zeileis et al., 2019).

To ensure that results were not driven by aggregating a binary variable (self-reported violence exposure) and a continuous variable (murder index), the harshness composite was rescored using a binary version of murder index dichotomized at 100 (which represents the national average). About 15% of participants resided in block groups that had higher than national average murder rates. Using this harshness composite, separate and simultaneous regression models were reconducted and presented in Supplementary Tables.

Results

The average participant was male (56%), aged 13 years ($SD = 2.50$). Fifty percent of the participants identified as White, 20% Black, 8%

https://doi.org/10.1017/S0954579421001577 Published online by Cambridge University Press

Table 1. Simple correlations among study variables ($N = 290$)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Age	–														
1. Race/ethnicity	−.01	–													
1. Gender	.09	−.01	–												
1. Severity	−.06	−.17*	.00	–											
1. Use of ICS	−.12*	.00	.00	.30*	–										
1. Use of BA	−.01	−.13*	.13*	.24*	.18*	–									
1. Harshness	.04	−.23*	−.15*	.00	−.11	.11	–								
1. Unpredictability	.11	−.13*	.04	.06	.03	.12*	.15*	–							
Stimulated cytokines															
1. Innate	−.18*	.02	.05	−.01	.09	.01	.10	−.08	–						
1. T1	−.10	−.14*	.00	.01	−.05	.08	.07	−.02	.22*	–					
1. T2	.12	−.16*	−.04	−.02	−.16*	−.08	.08	.06	−.02	.46*	–				
Glucocorticoid sensitivity															
1. Innate	.05	−.04	−.03	.06	.04	.01	−.10	−.01	−.08	.00	−.19*	–			
1. T1	−.01	−.06	.01	−.03	−.02	−.03	.04	.00	−.14*	−.07	−.13*	−.02	–		
1. T2	.05	−.03	−.04	−.01	.02	−.01	.02	.08	−.09	−.01	−.16*	.03	.48*	–	
1. Asthma control	.07	.08	−.22*	−.21*	−.08	−.39*	−.16*	−.11	−.10	.11	−.07	.01	.05	.10	–
1. Quality of life	.12*	.18*	−.19*	−.20*	.00	−.30*	−.19*	−.04	−.04	.08	−.08	.00	.04	.01	.73*

Note. *$p < .05$. Gender coded female = 0.5, male = −0.5, and race/ethnicity coded White = 0.5, non-White = −0.5. ICS refers to inhaled corticosteroid and BA refers to beta agonist. T1 and T2 refers to Type 1 and 2, respectively.

Asian, 8% Latino/a, and 14% identified with multiple races/ethnicities. Table 1 presents simple correlations among study variables. Of note, the correlation between harshness and unpredictability was small ($r = .15$), allowing examination of independent links to outcomes without concerns over multicollinearity issues.

Harshness and unpredictability in separate models

Table 2 presents regression results of harshness and unpredictability associations with immune and asthma outcomes.

Harshness and immune measures. Youth with greater harshness experiences had more stimulated production of innate pro-inflammatory cytokines ($b = .15$, $SE = .06$, $p = .019$) and were less sensitive to glucocorticoid inhibition of this response ($b = -.15$, $SE = .07$, $p = .027$). However, harshness was not associated with indices of adaptive immune response, namely the production of T1 or T2 cytokines, or their sensitivity to glucocorticoid inhibition.

Harshness and asthma outcomes. In terms of clinical asthma outcomes, youth with greater harshness experiences reported worse asthma control ($b = -.49$, $SE = .23$, $p = .036$) as well as lower quality of life ($b = -.20$, $SE = .07$, $p = .003$).

Unpredictability and immune measures. Unpredictability was not associated with stimulated production of innate pro-inflammatory or adaptive T1 and T2 cytokines. Unpredictability was also not associated with any measures of glucocorticoid sensitivity.

Unpredictability and asthma outcomes. Unpredictability was not associated with asthma control or quality of life.

Harshness and unpredictability in simultaneous models

Table 3 presents regression analyses with harshness and unpredictability as simultaneous predictors of immune and asthma outcomes.

Harshness. Independent of unpredictability, harshness remained significantly associated with more stimulated innate pro-inflammatory cytokine production ($b = .16$, $SE = .07$, $p = .014$) and lower sensitivity of this response to glucocorticoid inhibition ($b = -.15$, $SE = .07$, $p = .030$), as well as worse asthma control ($b = -.47$, $SE = .23$, $p = .046$), and lower quality of life ($b = -.20$, $SE = .07$, $p = .004$). Harshness remained unassociated with stimulated adaptive T1 and T2 cytokine production and the glucocorticoid sensitivity of these responses.

Unpredictability. Controlling for harshness, no significant associations were found between unpredictability and any immune measures or asthma outcomes.

Supplementary analyses

As summarized in Supplementary Tables S1 and S2, when harshness was assessed with a composite that used the continuous, rather than binary, measure of murder rate, pattern of results did not vary from the primary analyses. Specifically, in both separate and simultaneous models, harshness remained significantly associated with more stimulated production of innate pro-inflammatory cytokines (separate: $b = .21$, $SE = .09$, $p = .018$; simultaneous: $b = .20$, $SE = .09$, $p = .023$) and lower sensitivity to glucocorticoid inhibition of this response (separate: $b = -.17$, $SE = .08$, $p = .043$, simultaneous: $b = -.17$, $SE = .09$, $p = .046$), as well as worse asthma control (separate: $b = -.84$, $SE = .29$, $p = .004$, simultaneous: $b = -.83$, $SE = .29$, $p = .004$), and lower quality of life (separate: $b = -.29$, $SE = .09$, $p = .001$, simultaneous: $b = -.29$, $SE = .09$, $p = .001$).

Discussion

The current study found that harshness, but not unpredictability, was associated with asthma-relevant immune processes and

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Table 2. Separate regression analyses of harshness and unpredictability associations with immune measures and asthma outcomes ($N = 290$)

	Stimulated cytokines			Glucocorticoid sensitivity			Asthma outcomes	
	Innate	T1	T2	Innate	T1	T2	Asthma control	Quality of life
Harshness model								
Age	−.07 [−.11, −.03]*	−.04 [−.08, .00]	.04 [.00, .08]	.03 [−.02, .07]	.00 [−.05, .04]	.02 [−.02, .06]	.12 [−.03, .26]	.06 [.02, .11]*
White	.08 [−.15, .30]	−.22 [−.45, .01]	−.30 [−.54, −.06]*	−.12 [−.36, .13]	−.11 [−.35, .13]	−.04 [−.27, .19]	−.10 [−.83, .62]	.20 [−.04, .43]
Female	.16 [−.05, .36]	.03 [−.18, .24]	−.06 [−.29, .18]	−.11 [−.34, .12]	.05 [−.17, .27]	−.06 [−.26, .14]	−1.4 [−.21, −.70]*	−.42 [−.65, −.18]*
Severity	−.04 [−.18, .10]	−.02 [−.15, .11]	.01 [−.14, .16]	.05 [−.07, .17]	−.04 [−.17, .09]	−.02 [−.16, .12]	−.53 [−.96, −.09]*	−.18 [−.32, −.04]*
Use of ICS	.03 [−.01, .06]	−.02 [−.05, .02]	−.04 [−.08, −.01]*	.01 [−.03, .05]	.00 [−.04, .03]	.01 [−.02, .04]	.03 [−.09, .14]	.03 [−.01, .07]
Use of BA	−.01 [−.06, .05]	.03 [−.03, .08]	−.03 [−.08, .03]	.00 [−.05, .06]	−.01 [−.06, .03]	.00 [−.05, .05]	−.55 [−.74, −.36]*	−.12 [−.18, −.06]*
Harshness	.15 [.03, .28]*	.06 [−.07, .19]	.02 [-.12, .15]	−.15 [−.29, −.02]*	.04 [−.09, .18]	.04 [−.08, .17]	−.49 [−.95, −.03]*	−.20 [−.34, −.07]*
Unpredictability model								
Age	−.06 [−.11, −.02]*	−.04 [−.08, .01]	.04 [−.01, .08]	.02 [−.02, .07]	−.01 [−.05, .04]	.02 [−.03, .06]	.12 [−.02, .27]	.06 [.01, .11]*
White	.00 [−.22, .22]	−.25 [−.47, −.02]*	−.30 [−.52, −.08]*	−.06 [−.30, .18]	−.13 [−.36, .10]	−.04 [−.25, .17]	.06 [−.68, .79]	.28 [.05, .52]*
Female	.12 [−.09, .34]	.01 [−.21, .24]	−.06 [−.28, .16]	−.07 [−.31, .17]	.04 [−.19, .27]	−.07 [−.28, .14]	−1.3 [−2.0, −.55]*	−.37 [−.60, −.13]*
Severity	−.04 [−.17, .08]	−.02 [−.15, .11]	.01 [−.12, .14]	.05 [−.08, .19]	−.04 [−.17, .09]	−.02 [−.14, .10]	−.51 [−.93, −.09]*	−.18 [−.31, −.04]*
Use of ICS	.03 [−.01, .06]	−.02 [−.06, .02]	−.04 [−.08, −.01]*	.01 [−.03, .05]	.00 [−.04, .04]	.01 [−.03, .04]	.04 [−.09, .16]	.04 [.00, .08]
Use of BA	.00 [−.05, .05]	.03 [−.02, .09]	−.03 [−.08, .02]	.00 [−.06, .06]	−.01 [−.07, .04]	.00 [−.06, .05]	−.55 [−.73, −.37]*	−.13 [−.18, −.07]*
Unpredictability	−.08 [−.23, .07]	−.04 [−.19, .11]	.05 [−.10, .20]	−.04 [−.20, .13]	−.01 [−.17, .15]	.07 [−.08, .22]	−.29 [−.79, .21]	.00 [−.16, .16]

Note. *$p < .05$. Unstandardized regression coefficients [95% confidence intervals] are presented. Cluster-robust standard errors were presented for models with harshness as predictor to account for potential dependencies in neighborhood-level data. ICS refers to inhaled corticosteroid and BA refers to beta agonist. T1 and T2 refers to Type 1 and 2, respectively.

clinical outcomes. Specifically, children exposed to harsher environments had monocytes characterized by larger pro-inflammatory cytokine responses to a bacterial challenge and lower sensitivity to glucocorticoid signals which typically inhibit this response. In addition, children exposed to harsher environments were also more likely to have worse asthma control and lower asthma quality of life. These findings persisted even after controlling for the unpredictability of childhood environments. By contrast, unpredictability was not associated with any immune or asthma outcomes. These findings suggest that asthma-related immune processes and clinical outcomes may be more sensitive to the influence of harsh, rather than unpredictable, childhood environments.

The current findings are largely consistent with existing literature. For example, studies have linked other measures of childhood harshness, such as socioeconomic disadvantage and family stress, to cytokine production by innate and adaptive immune cells following in vitro challenges, as well as sensitivity to inhibition signals (Chen et al., 2007, 2017). In addition, previous studies have also linked various indicators of childhood harshness, including socioeconomic disadvantage, life stress, and maternal exposure to violence, to clinical measures of asthma, such as worse asthma control, greater activity limitations, and more symptoms (Bellin et al., 2015; Suglia et al., 2009; Thakur et al., 2014).

These findings also fit within evolutionary and life-history theories, which postulate that survival and the passing down of one's genes are fundamental goals of organisms and that environmental conditions shape organisms' biological and behavioral development to serve these goals. We hypothesized that greater harshness and unpredictability may signal immune cells to assume a state of heightened preparedness under these adverse environmental conditions by exhibiting a pro-inflammatory phenotype. The present study found support for this theory with respect to harshness and innate immune processes. That is, harsher environment was associated with immune cells exhibiting pro-inflammatory tendencies characterized by mounting more aggressive innate immune responses when challenged and having lower capacities in terminating these inflammatory processes. Adverse environmental conditions may have favored these characteristics because this phenotype should help eradicate pathogens more efficiently. However, aggressive and prolonged inflammatory responses can also contribute asthma symptoms. Supporting this notion, youth exposed to harsher environment had worse asthma control and lower quality of life.

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Table 3. Simultaneous regression analysis of harshness and unpredictability associations with immune measures and asthma outcomes ($N = 290$)

	Stimulated cytokines			Glucocorticoid sensitivity			Asthma outcomes	
	Innate	T1	T2	Innate	T1	T2	Asthma control	Quality of life
Age	−.07 [−.11, −.03]*	−.04 [−.08, .00]	.04 [.00, .08]	.03 [−.02, .07]	−.01 [−.05, .03]	.02 [−.03, .06]	.13 [−.02, .61]	.06 [.01, .11]*
White	.07 [−.15, .29]	−.22 [−.46, .01]	−.29 [−.53, −.05]*	−.12 [−.37, .13]	−.11 [−.36, .13]	−.03 [−.26, .20]	−.13 [−.86, .61]	.20 [−.03, .44]
Female	.17 [−.04, .37]	.03 [−.18, .24]	−.06 [−.30, .17]	−.11 [−.34, .12]	.05 [−.17, .27]	−.06 [−.26, .14]	−1.4 [−2.1, −.69]*	−.42 [−.65, −.18]*
Severity	−.04 [−.18, .10]	−.02 [−.15, .11]	.01 [−.14, .16]	.05 [−.07, .17]	−.04 [−.17, .09]	−.02 [−.16, .12]	−.52 [−.96, −.09]*	−.18 [−.32, −.04]*
Use of ICS	.03 [−.01, .06]	−.02 [−.05, .02]	−.04 [−.08, −.01]*	.01 [−.03, .05]	.00 [−.04, .03]	.01 [−.02, .04]	.03 [−.09, .15]	.03 [−.01, .07]
Use of BA	−.01 [−.06, .05]	.03 [−.02, .08]	−.03 [−.09, .02]	.00 [−.05, .06]	−.01 [−.06, .04]	−.01 [−.05, .04]	−.54 [−.73, −.35]*	−.12 [−.18, −.06]*
Harshness	.16 [.03, .29]*	.06 [−.07, .20]	.01 [−.12, .15]	−.15 [−.29, −.01]*	.05 [−.10, .19]	.04 [−.09, .16]	−.47 [−.93, −.01]*	−.20 [−.34, −.07]*
Unpredictability	−.05 [−.24, .05]	−.05 [−.19, .09]	.05 [−.09, .19]	−.02 [−.17, .13]	−.01 [−.15, .12]	.07 [−.06, .20]	−.23 [−.75, .28]	.02 [−.13, .17]

Note. *$p < .05$. Unstandardized regression coefficients [95% confidence intervals] are presented. Cluster-robust standard errors were presented to account for potential dependencies in neighborhood-level data. ICS refers to inhaled corticosteroid and BA refers to beta agonist. T1 and T2 refers to Type 1 and 2, respectively.

One additional hypothesis from the model by Ellis et al. (2009) is that harshness and unpredictability, being conceptually distinct dimensions, should have independent associations with developmental outcomes. In the present study, when controlling for unpredictability, harshness remained significantly associated with innate pro-inflammatory cytokine production, glucocorticoid regulation of this process, and clinical asthma outcomes. Unpredictability remained to be unrelated with immune and asthma outcomes after controlling for harshness. These findings indicate support for the independence hypothesis with respect to environmental harshness.

That harshness, but not unpredictability, may be associated with developmental outcomes is consistent with some previous findings. For example, one study examined the independent associations of harshness and unpredictability with adolescent life history strategy, assessed with sexual restrictedness, social deviance, and self-reported health (Brumbach et al., 2009). Results suggest that only harshness but not unpredictability was independently associated with less sexual restrictedness and more social deviance in adolescence. As such, there is some convergence with the current findings to suggest that harshness may be a stronger predictor. In addition, it is possible that harsh environmental conditions have stronger associations with childhood outcomes, whereas unpredictability may have stronger associations with adult outcomes, as suggested by the findings of a number of other studies that found independent links between unpredictability and adulthood outcomes (Brumbach et al., 2009; Simpson et al., 2012; Szepsenwol et al., 2017). However, this explanation is extremely speculative given the lack of existing research, and hence this proposition should be treated as preliminary until more substantial evidence emerges.

Why would innate immune processes, and clinical asthma outcomes, be more attuned to environmental harshness rather than unpredictability as suggested by current findings? One potential reason may be that harshness, being an environmental factor theorized to be relevant to morbidity, is more closely linked to survival than unpredictability is. Given that innate cells are the first-line defense against infections and injuries – and in some animal species, such as invertebrates, the only such defense – they may be more attuned to environmental signals regarding survival relative to uncertainty. That is, for these cells to recalibrate their operating tendencies, clear and sustained signs of risk to survival may be necessary. However, future research that examines the independent associations of harshness and unpredictability with immune outcomes is necessary to examine the replicability of the current findings.

Although harshness was associated with innate immune responses, it was not associated with adaptive (T1 or T2) immune responses. One explanation may be that harsh environments are more likely to calibrate innate immune cells, such as monocytes, rather than adaptive immune cells, such as T-helper cells, because it would be a more cost-efficient tradeoff. Specifically, mounting adaptive immune responses is more metabolically costly and maintaining them may take away resources from growth in other domains (McDade, 2005; Segerstrom, 2010). In addition, relative to the nonspecific responses that innate immune cells mount, the more targeted and powerful responses that adaptive immune cells mount may incur greater collateral damage to other tissues (Miller et al., 2011). As such, calibrating adaptive immune cells to have more aggressive response tendencies would not only be more energetically costly, but also perhaps more damaging to the body. However, because this study is among the few that examine both innate and adaptive immune responses, future research is necessary to ascertain the reliability of these specificity effects.

Strengths of this study include the large clinical sample of youths with asthma across a wide age range, the use of multiple indicators to assess environmental conditions, including neighborhood-level data, and the use of in-depth immune measures to model the operating tendencies of different classes of cells. This study is also among the few that related neighborhood-level exposures to cellular-level data to ask whether environmental conditions might get under the skin to impact immune functioning in the context of a chronic disease. However, there were also several limitations to this study. First, we relied on cross-sectional and correlational data; thus, although it is proposed that harshness and

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unpredictability would impact immune processes and clinical outcomes, neither causality nor directionality can be determined from our analyses. Future research would benefit from prospective designs that repeatedly assess environmental factors, immune processes, and clinical outcomes to better illustrate directionality of the links among these variables.

Second, our sample was relatively low-risk in terms of exposure to environmental harshness and unpredictability. The lack of variability in environmental conditions may have impacted results, rendering it difficult to interpret the null findings with regards to unpredictability (Young et al., 2020). Future research should utilize targeted recruitment to investigate whether the current findings would replicate in samples of high-risk youth.

Third, as data collection was conducted prior to the formulation of the research questions examined in the present study, measures of harshness and unpredictability were constructed using what was available. Thus, it is possible that effects that are postulated to be due to harsh environmental conditions from an evolutionary perspective are simply effects of exposure to violence that might not apply to other types of harsh conditions. Similarly, the current operationalization of unpredictability by family structural changes may have been limited, and others markers of unpredictability (e.g., changes specifically in the male parental figure) may have greater predictive value (Hartman et al., 2018). Recent theoretical work has also highlighted the need for more clarified conceptual definitions of unpredictability as well as more nuanced measurement of unpredictability, such as within-individual variance and within-individual autocorrelation of adverse experiences across time (Young et al., 2020). Future research would benefit from detailing the definitions and taxonomy of harshness and unpredictability to create theory-matching measures, which can be used to more systematically examine the veracity of conceptual models related to harshness and unpredictability.

Fourth, our immunology protocol only included one dose of hydrocortisone to model sensitivity to glucocorticoid inhibition. Future research should utilize multiple varying doses of hydrocortisone to model the within-individual slopes between hydrocortisone dose and cytokine production as a more reliable measure of the capacity of glucocorticoids to hamper cytokine production.

To conclude, environmental factors have pervasive effects on human development, and harshness and unpredictability have been postulated as two key environmental conditions. The present study found that harshness, but not unpredictability, was associated with innate immune processes and clinical asthma outcomes. We speculate that this may be because relative to ambiguous environments, harsh environments are more likely to signal threats to survival, triggering immune cells to enter a state of heightened preparedness that facilitates more aggressive responses to challenge and lower sensitivity to inhibition. Conceptualizing the present findings within the life history framework can help to elucidate why the body may have developed certain biological phenotypes despite the apparent health risks in the long run. If replicated, findings from this study would build on emerging work that relates core dimensions of childhood environment conditions to behavioral and biological processes that collectively can advance a theoretical understanding of human development.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579421001577.

Funding statement. This research was supported by National Institutes of Health grants awarded to EC (R01 HL108723) and PHL (F31 HL147509).

Conflicts of interest. The authors declare no conflicts of interest.

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