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Harsh Family Climate in Early Life Presages the Emergence of a Proinflammatory Phenotype in Adolescence

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Abstract

A growing body of evidence indicates that children reared in harsh families are prone to chronic diseases and premature death later in life. To shed light on the mechanisms potentially underlying this phenomenon, we evaluated the hypothesis that harsh families engender a proinflammatory phenotype in children that is marked by exaggerated cytokine responses to bacterial stimuli and resistance to the anti-inflammatory properties of cortisol. We repeatedly measured psychological stress and inflammatory activity in 135 female adolescents on four occasions over 1.5 years. To the extent that they were reared in harsh families, participants displayed an increasingly proinflammatory phenotype during the follow-up analyses. This phenotype was marked by increasingly pronounced cytokine responses to *in vitro* bacterial challenge and a progressive desensitization of the glucocorticoid receptor, which hampered cortisol's ability to properly regulate inflammatory responses. If sustained, these tendencies may place children from harsh families on a developmental trajectory toward the chronic diseases of aging.

Keywords

stress, inflammation, cortisol, family conflict, early life

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It has long been clear that children raised in risky families (i.e., families marked by conflict, a lack of emotional warmth, inadequate parenting, and household chaos) are prone to a broad array of adverse social and emotional outcomes (Cicchetti & Toth, 2005; Heim & Nemeroff, 2001). Recently, evidence has mounted to suggest that family climate early in life may also play a role in shaping people's susceptibility to chronic diseases later in life (Repetti, Taylor, & Seeman, 2002; Shonkoff, Boyce, & McEwen, 2009). For example, researchers who conducted the Adverse Childhood Experiences Study assessed the medical histories of more than 17,000 adults and found that rates of cardiovascular disease, autoimmune disorders, and premature death were 1.5 to 2.0 times higher among respondents who were exposed to familial violence, abuse, and neglect as children than among those who were not (see Anda et al., 2009; Dong et al., 2004; Dube et al., 2009). These patterns have been substantiated in experimental studies with animals (e.g., Ader & Friedman, 1965; Avitsur, Hunzeker, & Sheridan, 2006; Barreau, Ferrier, Fioramonti, & Bueno, 2004; Chida, Sudo, Sonoda, Hiramoto, & Kubo, 2007), which suggests that the patterns probably reflect causal effects of early experience on adult health (Cohen, Janicki-Deverts, & Miller, 2007).

These findings raise a difficult mechanistic question: How does a harsh family climate “get under the skin” in a manner that is sufficiently persistent to affect vulnerability to diseases that arise many decades later (G.E. Miller, Chen, & Cole, 2009)? One hypothesis advanced to answer this question suggests that harsh early-life family climates engender a phenotype characterized by exaggerated behavioral and biological responses to threatening stimuli (Cicchetti & Toth, 2005; Zhang et al., 2006). Biologically, this phenotype is thought to arise partly as a result of stressful early experiences causing desensitization of the glucocorticoid receptor. This desensitization enables greater outflow from the hypothalamic-pituitary-adrenocortical axis and the sympathetic nervous system, and it hampers the ability of cortisol to regulate the magnitude of inflammatory responses to infection and injuries (G.E. Miller, Chen, Fok, et al., 2009). This response pattern is thought to serve adaptive functions during acute threats to well-being, but, if activated chronically, it may exact an

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allostatic toll on the body that ultimately contributes to diseases of aging (McEwen, 1998; Shonkoff et al., 2009).

Evidence has been accruing to support the basic tenets of the hypothesis that harsh early-life family climates engender a phenotype that manifests in exaggerated responses to stress. To the extent that individuals are raised in harsher family climates, they display greater cardiovascular, neurohormonal, and inflammatory responses to stress as adults (e.g., Luecken & Lemery, 2004; Pace et al., 2006; Repetti et al., 2002). Consistent with the notion that this response pattern exacts a physiological toll on the body, studies have revealed that people from risky families also show higher blood pressure, worse metabolic profiles, and greater inflammatory activity than people from nonrisky families (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Lehman, Taylor, Kiefe, & Seeman, 2005; G.E. Miller, Chen, Fok, et al., 2009; Taylor, Lehman, Kiefe, & Seeman, 2006). All of these factors heighten people's risk for disease. Although these studies are provocative, two design features complicate interpretation of their findings. First, the studies typically relate early-life family climate to biological processes assessed on a single occasion in adulthood. This makes it difficult to ascertain temporal precedence and to evaluate whether early-life family climate has biological consequences that grow with time. Second, many of the studies that have assessed responses to stress have utilized laboratory paradigms (see reviews by Luecken & Lemery, 2004; Repetti et al., 2002), which are strong on internal validity but do not often correspond well with patterns seen in real life.

To gain further insights into these issues, we evaluated the exposure of a cohort of young women to real-life stressors over a period of 1.5 years. At each visit, we also assessed several processes involved with the regulation of inflammation and, using multilevel models, estimated the extent to which early-life family climate shaped trajectories of those regulatory processes over time. We predicted that to the extent that participants were reared in a harsh family environment, they would display evidence of an increasingly proinflammatory phenotype across the follow-up analyses. This trajectory would be marked by progressive desensitization of the glucocorticoid receptor, which would hamper cortisol's ability to regulate cytokine responses to bacterial challenge, thereby facilitating an increasingly proinflammatory condition. We also expected this phenotype to become most evident in response to psychological stress, such that in participants from harsh families, life events would activate inflammatory processes to a greater degree than in participants from nonharsh families.

Method

Participants

Data were collected as part of a larger project on depression and atherosclerosis in young women at risk for affective disorders. The participants were recruited from the Vancouver, British

Columbia, community through advertisements. Eligibility criteria included being female, 15 to 19 years old, fluent in English, free of acute illness in the 2 weeks preceding the study, without a history of chronic medical or psychiatric disorders, and at high risk for developing an initial episode of depression. High risk was defined as having a first-degree relative with a history of affective disorder or scoring in the top quartile of the population on cognitive vulnerability to depression.

Our study focused on 135 participants who completed assessments of early-life family climate. Table 1 summarizes the characteristics of these participants. They had a mean age of 17 years at study entry, were mainly of Asian or European descent, and generally came from well-educated families. The participants were reassessed on three further occasions, approximately 6, 12, and 18 months after study entry. The larger project was reviewed and approved by the University of British Columbia's Research Ethics Board. Written consent to participate in the study was obtained from all participants. For those younger than 18, a parent or guardian also provided consent.

Measures

Early-life family climate. To assess early familial experiences, we administered the Risky Families Questionnaire (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). This scale poses 13 questions regarding the harshness of the participant's family climate. Sample items include "How often did a parent or other adult in the household swear at you, insult you, put you down, or act in a way that made you feel threatened?" and "How often would you say that a parent or other adult in the household behaved violently toward a family member or visitor in your home?" When responding, participants were instructed to focus on the time prior to their entry in the study (i.e., from birth to age 14). Participants responded on a scale ranging from 1, *not at all*, to 5, *very often*. The Risky Families Questionnaire was internally consistent (Cronbach's $\alpha = .78$) in our sample.

Inflammatory parameters. Peripheral blood was drawn at each visit to assess three aspects of inflammation. First, the

Table 1. Characteristics of the Sample ($N = 135$)

| |
|--|
| Age: $M = 17.00$ years, $SD = 1.38$ |
| Race |
| Caucasian: 50.37% ($n = 68$) |
| East or South Asian: 41.48% ($n = 56$) |
| Other: 8.15% ($n = 11$) |
| Parental education: $M = 14.71$ years, $SD = 2.97$ |
| Daily cigarette smoker: 1.5% ($n = 2$) |
| Body mass index: $M = 21.61$ kg/m ² , $SD = 2.57$ |
| Alcohol use: $M = 2.11$ drinks/week, $SD = 4.29$ |
| Strenuous exercise: $M = 2.07$ hr/week, $SD = 1.96$ |
| Subjective sleep quality (1–4): $M = 3.01$, $SD = 0.51$ |
| Risky Families Questionnaire score (1–5): $M = 1.93$, $SD = 0.46$ |

extent of systemic inflammatory activity was quantified via serum levels of interleukin-6 (IL-6). This molecule plays a key role in orchestrating chronic inflammatory responses and is often used to index ongoing immune activation (A.H. Miller, Maletic, & Raison, 2009). IL-6 levels were measured twice with commercially available high-sensitivity enzyme-linked immunosorbent assay (ELISA) kits (HS600B; R&D Systems, Minneapolis, MN), which have a minimum detection threshold of 0.039 pg/ml and inter- and intra-assay variability of less than 10%.

Second, to assess the capacity of participants' white blood cells to respond to microbial challenge, we cultured the cells with a bacterial stimulus, lipopolysaccharide (LPS). When immune cells encounter LPS, they secrete proteins, such as IL-6, which help clear infections and heal injuries. Although this response is critical for survival, its magnitude and duration must be carefully regulated, because excessive inflammation contributes to chronic diseases. This assay quantified how aggressively participants' white blood cells responded to a fixed dose of LPS. Whole blood was drawn into lithium-heparin Vacutainers (Becton-Dickinson, Oakville, Ontario, Canada), diluted in a 10:1 ratio with saline, and incubated with LPS (50 ng/ml; Sigma, St. Louis, MO) for 6 hr at 37 °C in 5% carbon dioxide (CO₂). The supernatants were collected and frozen at -80 °C until analysis. IL-6 was measured twice with DuoSet ELISA Development Systems kits (R&D Systems, Minneapolis, MN), which have a minimum detection threshold of 0.7 pg/ml and inter- and intra-assay variability of less than 5%.

Third, to measure sensitivity to signals that regulate inflammation, we quantified IL-6 production in cells that had been co-incubated with LPS and cortisol. Cortisol conveys anti-inflammatory messages to immune cells, and the third assay measured their ability to respond to these signals by dampening IL-6 production. Blood was diluted in a 10:1 ratio with saline and dispensed into culture plates (Sigma Chemicals, St. Louis, MO) with LPS (50 ng/ml). Doses of hydrocortisone were added to four of the wells in varying concentrations (2.76×10^{-5} M, 2.76×10^{-6} M, 2.76×10^{-7} M, 2.76×10^{-8} M). The fifth well contained only the blood and saline solution. After 6 hr of incubation at 37 °C in 5% CO₂, the supernatants were collected and frozen until analysis. IL-6 levels were measured twice using DuoSet ELISA Development Systems kits (R&D Systems). Dose-response curves were later generated for each subject's data. From the dose-response curves, we calculated the concentration of hydrocortisone needed to diminish IL-6 production by 50% (i.e., the log inhibitory coefficient-50, or log IC₅₀). This value is inversely proportional to glucocorticoid sensitivity, meaning that higher values indicate that immune cells are less sensitive to cortisol's anti-inflammatory signals.

Episodic stressors. At each visit, we administered the UCLA Life Stress Interview—Adolescent Version (Adrian & Hammen, 1993). This semistructured interview covers acute and chronic

forms of stress over the past 6 months of the participant's life. The interviewer asks a series of open-ended questions about family, friends, school, and health to gather details about episodic stressors, which are defined as specific events with a discrete onset and offset. To judge the objective impact of episodic stressors, our team established a consensus rating for each event after being briefed on its details by the primary interviewer. Impact ratings ranged from 1, *no long-term impact*, to 5, *severe long-term impact*. The ratings explicitly considered the context in which each event occurred. For example, if a participant's grandfather had a heart attack, the impact rating would depend on factors such as the closeness of the relationship between the participant and the grandfather, whether she visited him in the hospital, and whether she had previous experience coping with serious family illnesses. Following convention, we considered episodic stressors rated 2.5 or higher, *moderate long-term impact*, to be major events (G.E. Miller & Chen, 2006).

Alternative explanations. We assessed several other variables that might provide alternative explanations for any associations between family climate and proinflammatory phenotype. These variables included demographic (age; ethnicity; socioeconomic status, or SES) and biobehavioral (smoking, total adiposity, physical activity, alcohol use, sleep quality) factors known to covary with or directly modulate inflammatory processes (O'Connor et al., 2009), as well as symptoms of depression. SES was indexed by the highest educational degree achieved by the participant's mother or father. Smokers were classified as persons consuming more than 10 cigarettes daily, and adiposity was measured as body mass index (BMI; kilograms/meter²). Physical activity was measured as minutes each week engaged in "regular activity akin to brisk walking, jogging, bicycling, etc., long enough to work up a sweat" (Paffenbarger, Blair, Lee, & Hyde, 1993, p. 63). Alcohol use was quantified as the number of drinks per week, and subjective sleep quality was rated on a scale from 1 to 4, using a well-validated instrument (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). In preliminary analyses, we established that all of these factors, except BMI, were stable over the follow-up period. Hence, we averaged values across visits and used these aggregates as covariates. Because BMI increased significantly over the course of the study, $F(3, 315) = 4.85$, $p = .003$, it was modeled as a time-varying covariate. Finally, depressive symptoms were assessed at each visit using the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and these scores were used to determine whether low mood inflated the observed associations.

Results

Statistical approach

To determine whether early-life family climate presaged changes in inflammatory processes, we estimated a series of

growth-curve models with hierarchical linear modeling (HLM 6.03; Raudenbush, Bryk, & Congdon, 2006). In the within-person (or Level 1) models, we estimated outcomes as a function of months from study entry, BMI, and a residual term. These models yielded a series of person-specific intercepts reflecting outcomes at study entry (b_{0i}) and person-specific trajectories reflecting the rate of change over the 1.5-year follow-up period (b_{1i}). In the between-person (or Level 2) models, we estimated b_{0i} and b_{1i} values for each participant as a function of age, ethnicity, SES, physical activity, alcohol use, sleep quality, and early-life family climate. (Smoking was not included as a covariate because only 2 participants engaged in it regularly.) The Level 2 models also included random variables specifying the amounts by which each participant deviated from the sample's average b_{0i} and b_{1i} .

Preliminary analyses

We began by estimating simple Level 1 models to describe patterns of change. During the follow-up period, the sample as a whole displayed a significant increase in stimulated IL-6 production ($b_{10} = 215$, $SE = 76$, $p = .006$), but the other two outcomes, sensitivity to cortisol inhibition and the extent of systemic inflammation, remained stable over time ($ps = .66$ and $.24$, respectively; see Table 2). However, analyses revealed significant variability around these samplewide estimates ($ps < .005$), suggesting that participants differed reliably in their trajectories over time. In the next set of models, we added BMI to Level 1 equations. BMI covaried with systemic inflammation over time such that as a woman's BMI increased, so did her level of IL-6 in circulation ($b_{10} = 0.06$, $SE = 0.02$, $p = .01$). BMI was not associated with stimulated production of IL-6 or sensitivity to cortisol inhibition ($ps < .49$).

Early-life family climate

On the basis of these findings, we estimated another series of models exploring whether early-life family climate

Table 2. Levels of Inflammatory Parameters at Study Entry and Follow-Up

| Visit | Circulating IL-6 (pg/ml) | | Production of IL-6 following LPS stimulation (pg/ml) | | Resistance to glucocorticoids (log IC ₅₀) | |
|-------|--------------------------|------|--|--------|---|------|
| | Mean | SD | Mean | SD | Mean | SD |
| 1 | 0.68 | 0.66 | 43,235 | 15,239 | -6.43 | 0.33 |
| 2 | 0.77 | 0.81 | 48,077 | 16,678 | -6.45 | 0.27 |
| 3 | 0.75 | 0.92 | 46,174 | 17,084 | -6.46 | 0.28 |
| 4 | 0.74 | 0.71 | 48,013 | 16,116 | -6.45 | 0.27 |

Note: Visit 1 is study entry; Visits 2, 3, and 4 occurred approximately 6, 12, and 18 months after study entry, respectively. IC₅₀ (inhibitory coefficient-50) is the concentration of hydrocortisone needed to diminish interleukin-6 (IL-6) production by 50%. LPS = lipopolysaccharide.

predicted variability in inflammatory trajectories above and beyond the effects of potential confounds (i.e., BMI at Level 1 and age, ethnicity, SES, physical activity, alcohol use, and sleep quality at Level 2). The results of these analyses are displayed in Table 3. The confounds were not consistently associated with inflammatory parameters at study entry or with the rate at which inflammatory parameters changed over the follow-up period. However, early-life family climate was a significant predictor of the trajectories for IL-6 production ($p = .01$) and cortisol sensitivity ($p = .04$). To the extent that participants were reared in a harsh family environment, they displayed increasing stimulated IL-6 production over the follow-up period and decreasing sensitivity to cortisol's anti-inflammatory properties (see Fig. 1). In terms of effect size, family climate accounted for 24.70% of the between-participants variance in trajectories of IL-6 production, once the contribution of demographic and biobehavioral factors were removed. The corresponding figure for cortisol-sensitivity trajectories was 7.48%. Family climate was not associated with trajectories of systemic inflammation as reflected in circulating IL-6 ($p = .75$) or with any of the outcomes at the time of study entry ($ps > .13$).

We considered two alternative explanations for these findings. The first was that low mood was inflating the observed associations, by biasing participants' recall of their early family life and simultaneously activating proinflammatory circuits (G.E. Miller & Blackwell, 2006; A.H. Miller et al., 2009). To evaluate this possibility, we conducted another wave of analyses, in which symptoms of depression were added to Level 1 models as a time-varying covariate. Early-life family climate continued to be a significant predictor of IL-6-production trajectories ($p = .02$) and a marginal predictor of cortisol-sensitivity trajectories ($p = .08$), a result suggesting that low mood played little role in these associations. The second alternative explanation had to do with the timing of assessments. Because the Risky Families Questionnaire was added to the project after we began recruiting participants, there was some between-person variability in the timing of its administration. However, the timing of administration was unrelated to scores on this questionnaire ($r = .09$, $p = .33$) and was not associated with trajectories of any of the inflammatory parameters ($ps > .39$). There was also no evidence of interactions between scores on the questionnaire and timing of administration for any of the inflammatory trajectories ($ps > .27$).

Responsivity to stress

The final models explored whether being reared in a harsh family climate accentuated participants' inflammatory responses to life stress. This hypothesis was evaluated using another series of growth-curve models, which were identical in structure to the previous models except that a binary, person-centered variable was added to Level 1, reflecting exposure to a major event over the preceding 6 months. The analyses revealed a significant interaction between harsh family climate and life stress in

Table 3. Level 2 Predictors of Inflammatory Parameters at Study Entry and Over Time

| Predictor | Production of IL-6 following LPS stimulation | | | Resistance to glucocorticoids (log IC ₅₀) | | | Circulating IL-6 | | |
|-------------------|--|-------|-----|---|------|-----|----------------------------|------|-----|
| | Unstandardized coefficient | SE | p | Unstandardized coefficient | SE | p | Unstandardized coefficient | SE | p |
| Baseline | | | | | | | | | |
| Constant | 42.99 | 17.83 | .01 | -645 | 5.00 | .01 | 0.62 | 0.09 | .01 |
| Age | -1.33 | 1.06 | .21 | 0.09 | 3.43 | .97 | 0.00 | 0.10 | .98 |
| Race | 4.31 | 3.04 | .16 | 2.01 | 8.53 | .81 | 0.25 | 0.15 | .10 |
| SES | 0.41 | 1.24 | .74 | 0.42 | 2.29 | .86 | -0.01 | 0.06 | .99 |
| Exercise | 0.68 | 0.63 | .28 | 0.65 | 1.23 | .60 | -0.08 | 0.06 | .13 |
| Alcohol use | -0.02 | 0.26 | .94 | 0.76 | 0.56 | .18 | 0.29 | 0.25 | .26 |
| Sleep quality | 1.37 | 2.68 | .61 | 1.66 | 6.55 | .80 | 0.11 | 0.08 | .17 |
| Harsh family | -1.04 | 1.22 | .39 | -3.65 | 3.25 | .27 | -0.08 | 0.05 | .13 |
| Trajectory | | | | | | | | | |
| Constant | 0.26 | 0.98 | .01 | 0.01 | 0.37 | .36 | 0.01 | 0.01 | .29 |
| Age | 0.02 | 0.05 | .79 | 0.04 | 0.03 | .20 | 0.01 | 0.01 | .45 |
| Race | -0.10 | 0.15 | .35 | -0.04 | 0.06 | .56 | -0.00 | 0.02 | .94 |
| SES | -0.12 | 0.07 | .11 | -0.05 | 0.03 | .09 | -0.01 | 0.01 | .74 |
| Exercise | -0.03 | 0.03 | .34 | 0.01 | 0.01 | .34 | 0.00 | 0.01 | .97 |
| Alcohol use | -0.01 | 0.02 | .71 | 0.00 | 0.00 | .99 | -0.02 | 0.02 | .31 |
| Sleep quality | -0.35 | 0.17 | .05 | -0.44 | 0.53 | .41 | 0.01 | 0.01 | .39 |
| Harsh family | 0.23 | 0.09 | .01 | 0.60 | 0.29 | .04 | 0.00 | 0.01 | .75 |

Note: In Level 1 models, the outcomes were predicted from time (coded in months from study entry) and from body mass index. Race was coded as 1 (White) or 0 (other). All other variables were grand-mean-centered. IC₅₀ (inhibitory coefficient-50) is the concentration of hydrocortisone needed to diminish interleukin-6 (IL-6) production by 50%. LPS = lipopolysaccharide; SES = socioeconomic status.

predicting IL-6 production ($b_{21} = 4.68$, $SE = 1.21$, $p = .001$). Figure 2 shows that, among participants raised in harsh family climates, IL-6 production was higher if they had experienced a major life event in the preceding 6 months than if they had not experienced such an event. By contrast, participants raised in nonharsh family climates showed little change or a slight decline in IL-6 production after being exposed to a major life event. These effects were above and beyond the contribution of demographic and biobehavioral confounds. They also were not a function of participants from harsh family climates simply experiencing more frequent or impactful events: Scores on the Risky Families Questionnaire were only weakly related to the number and severity of episodic stressors over the course of the study ($r_s = .14$, $p_s = .10$).

Because participants from harsh family climates will, by definition, experience more conflict and violence at home than other participants do, we reran these analyses excluding any events that centered on family difficulties. The interaction between family climate and life stress persisted under these conditions ($b_{21} = 3.70$, $SE = 1.26$, $p = .004$). Thus, there appears to be a broad tendency toward enhanced reactivity to stress among participants from harsh family climates. There were no significant interactions between family climate and life stress in predicting the other inflammatory outcomes ($p_s > .47$).

Discussion

A growing body of evidence indicates that children raised in risky families are vulnerable to chronic disease when they reach the later decades of life (Repetti et al., 2002; Shonkoff et al., 2009). Although the mechanisms underlying this phenomenon are not well understood, one attractive hypothesis is that harsh family climates engender a proinflammatory phenotype, which over time takes an allostatic toll on the body (Cicchetti & Toth, 2005; G.E. Miller, Chen, Fok, et al., 2009; Zhang et al., 2006). Our data provide support for this notion by showing that, over a 1.5-year period, young women who were raised in risky families displayed increased IL-6 responses to two different types of threatening stimuli, an in vitro challenge with bacterial products and a real-life psychological stressor. Over this period, participants also showed progressive desensitization of the glucocorticoid receptor, such that their immune cells exhibited increasing resistance to anti-inflammatory signals from cortisol.

These findings converge with those of other studies that have revealed increased inflammatory activity in adults reared in unfavorable circumstances (Danese et al., 2007; G. Miller & Chen, 2007; G.E. Miller, Chen, Fok, et al., 2009; Taylor, Lehman, et al., 2006). Our findings also extend previous research by showing that the magnitude of this disparity grows

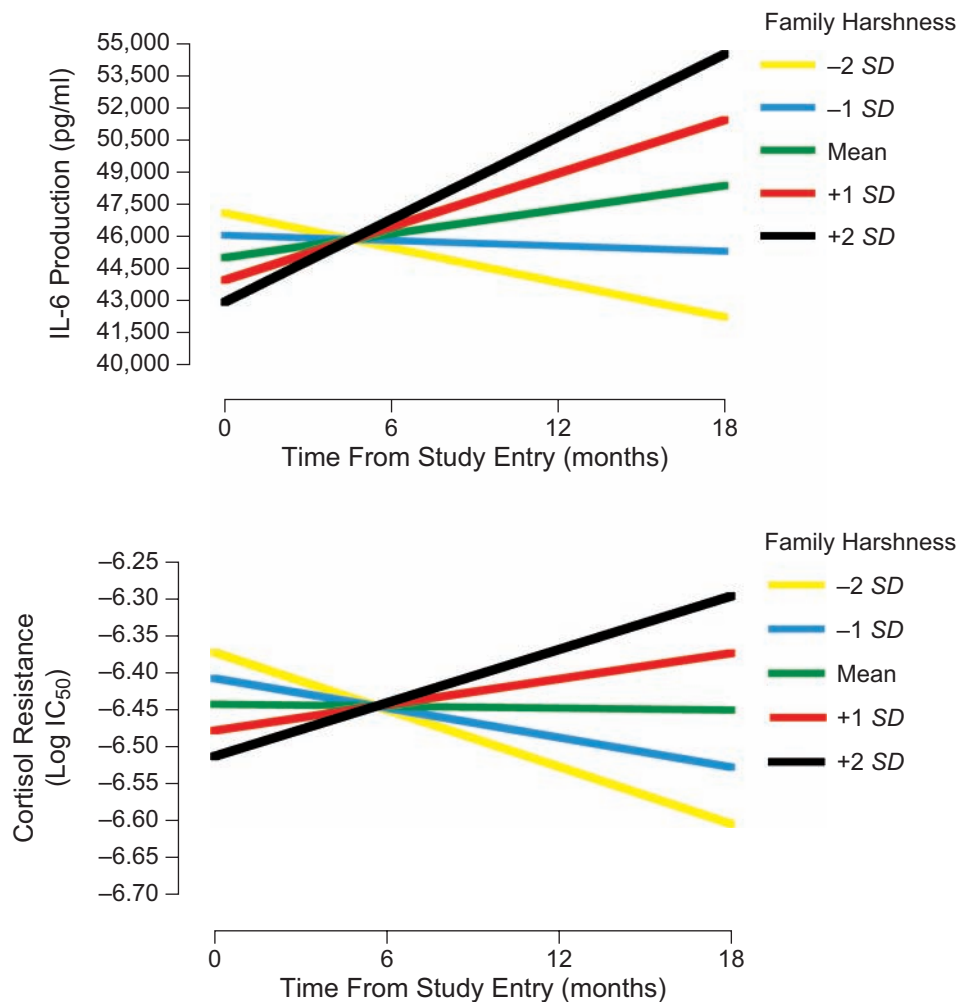


Fig. 1. Early-life family climate and inflammatory trajectory in adolescence. The graphs show changes in participants' interleukin-6 (IL-6) production in response to stimulation with lipopolysaccharide (upper panel) and in participants' cortisol resistance (lower panel) over the course of the study. The predicted values are shown at five different levels of family harshness. Log IC₅₀ = log inhibitory coefficient-50.

with time, such that youths from harsh families are set upon a trajectory of exaggerated proinflammatory responding and partial resistance to glucocorticoid signaling. It is unclear why this disparity was not apparent at study entry but only gradually appeared during the follow-up period. Because the women in our sample were 15 to 19 years of age at the onset of the study, menarche-induced changes in immune functions are unlikely to be responsible for our results. However, puberty sets into motion hormonal cascades that continue to promote maturation throughout adolescence (Dahl, 2004), and it is conceivable that these hormonal changes underlie our findings. Identifying these cascades and how they modulate immunity needs to be a focus of future research.

Our study also highlights desensitization of the glucocorticoid receptor as one mechanism potentially underlying the proinflammatory phenotype. Cortisol is a powerful regulator of the transcriptional-control pathways that orchestrate

immune responses to infection and injuries (Webster, Tonelli, & Sternberg, 2002). To the extent that familial harshness impairs the immune system's capacity to transduce cortisol-mediated signals (e.g., through glucocorticoid-receptor desensitization), the immune system would be expected to mount larger inflammatory responses to microbial challenge and be slower to terminate them. In the short term, this pattern might benefit people's health by protecting them against infections. However, over the long term, it would foster a low-grade inflammatory state (G.E. Miller, Cohen, & Ritchey, 2002; Raison & Miller, 2003) that contributes to aging-related conditions such as metabolic syndrome, autoimmune disorders, and cardiovascular disease (Nathan, 2002).

Our study also extends previous research by showing that even normative variations in early-life family climate can shape the evolution of response tendencies in the immune system. We assessed harshness on a 5-point continuum. For each

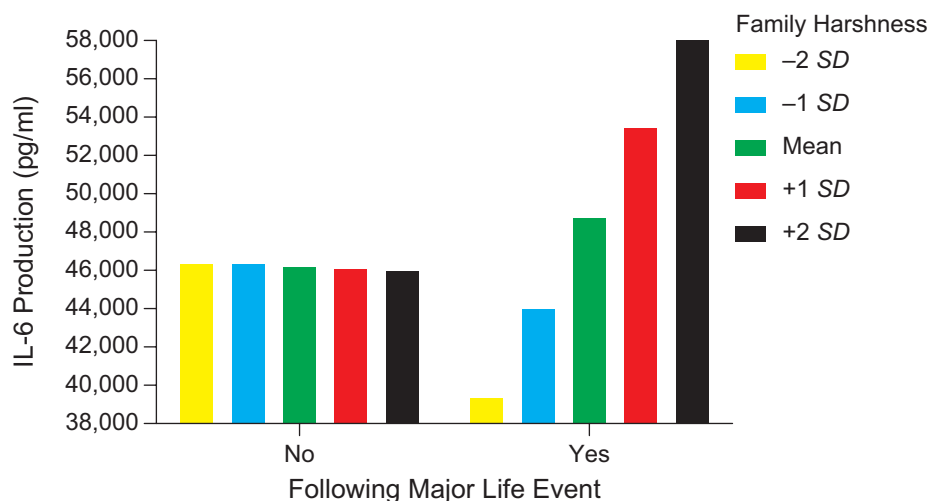


Fig. 2. Participants' interleukin-6 (IL-6) production in response to stimulation with lipopolysaccharide. The graph shows levels of IL-6 production following major life events (right side) and levels of IL-6 production not following major life events (left side). The predicted values are shown at five different levels of family harshness.

half-point increment in harshness, there was a 10% increase in stimulated IL-6 production over time and a 4% decline in sensitivity to cortisol. These patterns suggest that there is a good deal of plasticity in the response tendencies of monocytes (the cells that engage LPS and secrete IL-6) and that even mild exposure to a risky family in early life can shift the developmental trajectory toward a proinflammatory phenotype.

Although a harsh family climate presaged changes in stimulated cytokine production and sensitivity to cortisol, there was no evidence that it was associated with the degree of ongoing inflammatory activity, as marked by serum IL-6. These findings suggest that harshness affects leukocytes' response to microbial challenge but does not affect their production of cytokines under quiescent conditions. This discrepancy may reflect the fact that in young people, the immune system's response to inhibitory molecules such as cortisol is relatively intact, which prevents the kind of overshooting that would foster ongoing inflammation. However, our data suggest that as women from harsh families age, they will show larger cytokine responses to microbial challenge and become progressively more resistant to cortisol-mediated inhibition. Over time, such tendencies could favor the kinds of ongoing inflammatory activity seen in adults who faced early-life maltreatment (Danese et al., 2007; Taylor, Lehman, et al., 2006).

Four limitations of this study need to be considered. First, it used participants' self-reports of early-life family climate, and the veridicality of these reports was not ascertained through collateral sources. Thus, it is possible that our measure captured something different from what we intended, such as participants' reconstructed memories of their early family lives or self-descriptions that they had enhanced to be more socially desirable. However, even if our self-report measure did not capture what we intended, this work would still be valuable,

because similar self-reports (e.g., Anda et al., 2009; Dong et al., 2004; Dube et al., 2009) have been linked to excess morbidity and mortality. Thus, the phenomena that they capture, whether accurate reflections of early life or reconstructed versions of it, seem to be important for long-term health.

The second limitation of this study is its observational design, which makes it impossible to derive causal inferences about the effects of early-life family climate. Although we used covariance analyses to eliminate the most plausible alternative explanations, other (unassessed) factors may have contributed to the observed associations. The third limitation is that our findings come from young women at risk for affective disorders; such women are more likely than the general population to have been reared in a harsh family climate and are probably more sensitive to its effects. Thus, further research is needed to determine how generalizable the findings are to the broader population. Finally, the study focused on a narrow window of time in the life course, 1.5 years of adolescence, and it is unclear how representative the trajectories we observed are of other periods of life.

Collectively, these limitations suggest that our results should be considered preliminary until they have been substantiated in studies with representative samples, long-term prospective designs, and more thorough assessments of potential confounders. In future research, it will be important to further characterize the elements of the phenotype we observed and ascertain how those elements might together influence habitual patterns of responding to threatening stimuli. Particularly relevant to this endeavor are data showing that children from riskier families are more vigilant for cues that connote anger and threat (Chen, Langer, Raphaelson, & Matthews, 2004; Pollak, 2008). These children seem to remain vigilant for such cues into adulthood, perhaps as a result of experience-dependent remodeling

of the amygdala or the prefrontal circuitry that regulates the amygdala (Gianaros et al., 2008; Taylor, Eisenberger, et al., 2006). Research that explicates how these vigilant tendencies modulate the function of other bodily systems (e.g., metabolic, cardiovascular, immune), and what implications that modulation has for disease, would be especially valuable.

Despite its limitations, the present study provides insights into mechanisms through which early-life family climate might come to shape later risk for chronic disease. Through further research, we should soon be able to construct multi-level models that depict how the social context a child is reared in “gets under the skin” to shape long-term health.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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