Respiratory Sinus Arrhythmia as a Physiological Resilience Marker for Children's Health

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ABSTRACT

Objective: The current study aimed to test parasympathetic nervous system activity, indexed through resting respiratory sinus arrhythmia (RSA) as a resilience factor that moderates the associations between socioeconomic status (SES), circulating cytokines, and somatic health in children.

Methods: The sample included 181 parent-child dyads (mean [standard deviation] child age = 9.91 [0.57] years; 50.3% boys). Parents reported on family income, parental education, and subjective social status, to index SES. Children provided serum samples for assaying circulating inflammatory cytokines and had RSA measured during a 5-minute seated resting period. We used a composite measure of inflammation that combined standardized measures of interleukin 6, interleukin 10, and tumor necrosis factor α. Parents reported on their child's global health impairment and number of chronic health conditions.

Results: Lower SES was associated with poorer global health, and higher levels of inflammation were associated with poorer global health, but these associations were not significant among children with high resting RSA. Specifically, resting RSA moderated the association between SES and global health impairment ($B = 0.09$, standard error [SE] = 0.02, $p < .001$). Preliminary evidence suggests that resting RSA may also moderate the association between inflammation and global health impairment ($B = -0.12$, SE = 0.03, $p < .001$), although this effect was no longer significant after Winsorizing an outlier value of a child with high global health impairment ($B = -0.06$, SE = 0.03, $p = .04$).

Conclusions: High resting RSA may represent a physiological profile of resilience in children, weakening the associations between low SES and poor somatic health, and between greater inflammation and poor somatic health.

Key words: socioeconomic status, inflammation, cytokines, respiratory sinus arrhythmia, health.

INTRODUCTION

Childhood socioeconomic disadvantage is associated with poorer physical health (1). Children raised in low-socioeconomic-status (SES) environments are rated by parents as having poorer global health (2,3) and have higher rates of chronic health conditions and all-cause mortality (for a review, see Ref. (4)). Low childhood SES also forecasts poorer health later in the life span. Low SES in childhood is associated with poorer global health (5) and a greater risk of noncommunicable diseases (6) in adulthood.

Leading conceptual models suggest that increased psychosocial stress exposure associated with socioeconomic adversity and the resulting chronic activation of stress physiology may explain why children in lower-SES environments exhibit poorer health (1). Chronic activation of neural and autonomic circuits of threat appraisal can lead to excessive wear and tear on bodily organs (i.e., allostatic load; (7)), as well as elevated systemic inflammation, which is associated with higher rates of health disorders (e.g., cardiovascular disease; (8)) and poorer global health (9,10). In line with this, low early-life SES is associated with elevated levels of circulating inflammatory cytokines in both adult (11) and youth samples (12,13).

However, despite the rather robust association between childhood SES and health, not all children who experience childhood economic adversity exhibit poor health (1,14). A more nuanced understanding of why some children show resilience, or positive adaptation, in the face of socioeconomic disadvantage could lead to the discovery of novel intervention methods (15).

Investigations into protective factors in the association between SES and health have begun to examine physiological profiles associated with more adaptive responding to environmental threat and challenge (16). An individual with a more flexible physiological response profile, who rapidly recovers after threat-induced activation, may exhibit resilience—that is, better than expected adaptation in the context of adversity (17). Accumulating developmental evidence supports a link between autonomic nervous system activity, particularly parasympathetic activity, and affective resilience (17).

Parasympathetic nervous system (PNS) activity, as indexed through resting respiratory sinus arrhythmia (RSA), has emerged as a promising marker of an individual's propensity to physiologically respond to challenge (18). Specifically, high resting RSA is associated with more flexible and adaptive responding, greater emotion regulation, and better general psychosocial functioning (19,20). In addition, PNS activity has been implicated in the

BMI = body mass index, **ECG** = electrocardiogram, **FDR** = false discovery rate, **HR** = heart rate, **IL-6** = interleukin 6, **IL-8** = interleukin 8, **IL-10** = interleukin 10, **PNS** = parasympathetic nervous system, **RSA** = respiratory sinus arrhythmia, **SES** = socioeconomic status, **TNF-α** = tumor necrosis factor α

SDC Supplemental Digital Content

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modulation of inflammation (21), such that higher resting RSA is associated with lower circulating cytokine levels in adults (22), as well as smaller increases in cytokine levels during challenge in children (23). In rodent models, stimulation of the vagus nerve leads to better disease prognosis and survival after experimentally induced inflammatory disease (21), suggesting the PNS may moderate the link between inflammation and disease.

These combined findings suggest that high resting RSA may reflect a physiological profile of resilience in the association between SES and somatic health. Specifically, high resting RSA may promote resilience by a) promoting flexible responding to challenge and therefore reducing instances of prolonged physiological activation in high chronic stress environments, and b) modulating inflammatory processes. The role of parasympathetic modulation of inflammation may also be multifaceted. For example, high resting RSA may be associated with reduced production of inflammatory cytokines in response to chronic stress, leading to a weaker association between chronic stress and baseline cytokine levels, as well as better management of circulating cytokines, which would lead to a weaker association between baseline cytokine levels and health.

High resting RSA in children has been found to weaken the associations between low SES and poor inhibitory control (24) and between interparental conflict and poorer child health (25). However, we are currently only aware of one previous study that tested RSA as a moderator of the association between SES and health in children. In this study, kindergarteners' RSA reactivity during challenge moderated the association between SES and global health, such that the link between lower SES and poorer health was only observed for children who exhibited high RSA reactivity (26). However, high RSA reactivity is not always a risk factor. For example, a different study in adults found that insecure attachment predicted poor health, but only for individuals who exhibited low RSA reactivity (5). These inconsistent findings reflect the context-dependent association between RSA reactivity and adaptive responding (27). Investigating resting parasympathetic activity as a moderator between SES and health in children could complement the mixed findings with RSA reactivity. In addition, further research is needed on the role of RSA as a moderator of the links between SES and inflammation, and between inflammation and health in childhood.

Current Study

The current study aimed to test the associations between SES, health, and basal inflammation in late childhood and to investigate resting RSA as a moderator of these associations. As such, we had three hypotheses. First, we hypothesized that lower SES would be associated with poorer global health, higher prevalence of chronic health conditions, and higher levels of inflammation. Second, we hypothesized that children with higher levels of inflammation would have poorer global health and greater prevalence of chronic health conditions. Lastly, we hypothesized that resting RSA would moderate these associations, such that the associations between SES, health, and inflammation would be weaker for children who exhibited high resting RSA.

METHODS

Participants

One hundred eighty-two children aged 9 to 11 years were recruited to take part in the present study. One participant ended the session shortly after arrival at the laboratory, before providing any data. This resulted in a final sample of $N = 181$ participants, including 91 who identified as male, 88 who identified as female, and 2 who identified as nonbinary (92 male and 89 female at birth; mean [standard deviation {SD}] age = 9.91 [0.57] years). Participants were 64.2% White, 24% mixed race/ethnicity, 5.6% Asian, and 6.2% other race/ethnicity (non-White Hispanic or Latino, Native American or Alaska Indigenous, Black or African American). Participants' families had an average yearly income of $120,600 (SD = $59,000). To avoid conducting experiments with participants who were ill, the following steps were taken. The day before the study visit and the day of the study visit, participants' parents were contacted and asked if their child was currently or had been recently sick. If this was the case, the experiment was rescheduled to 2 weeks after symptoms had fully subsided. The study was approved by the institutional review boards of the University of California, Davis, and the State of California Committee for the Protection of Human Subjects. Data collection took place between August 2017 and January 2020.

Study Procedure

Participating children and a parent or guardian arrived at the laboratory between 1:00 PM and 2:30 PM. Informed consent and assent were obtained upon arrival from parents/guardians and children, respectively. The current study was part of a larger study of social-emotional development and health, which included random assignment to experimental manipulation, previously reported elsewhere (28). The current study examined individual differences in baseline data across all participants, which were thus independent of subsequent experimental manipulation. Thirty minutes after arrival at the laboratory, a subset of children provided a basal serum sample (see discussion hereinafter for details on serum extraction procedure); an hour after arrival, children were fitted with an ambulatory electrocardiogram (ECG) for the collection of physiology data. Children had their height and weight measured by an experimenter using a physician scale and stadiometer, for the calculation of body mass index (BMI).

Serum Collection and Processing Procedure

A subsample of 132 participants of the total sample were invited to provide serum data for assaying cytokine levels. Basal serum, collected 30 minutes after arrival to the laboratory, was used in the present analysis. The blood collection was part of a feasibility study aimed at determining how difficult it would be to collect multiple intensive biological markers in participants of this age range. Blood draws were collected by trained phlebotomists. Samples were inverted gently five times and then left to clot in serum separator tubes for 60 minutes, after which samples were centrifuged at 2700 rpm for 10 minutes. Blood samples were then aliquoted into microvials and stored at −80°C, until being shipped to Northwestern University for assaying. Of the 132 children invited to participate in the additional serum collection procedure, 29 children did not provide blood samples (14 participants declined to participate, the phlebotomist had a scheduling conflict for 13 visits, and the phlebotomist was unable to draw sufficient blood from 2 participants). This resulted in a sample of $n = 103$ children with available serum data. Within the total study sample, participants who provided serum data did not significantly differ from participants who did not provide serum data, in any variable used in the current analysis (p values > .10).

Measures

Socioeconomic Status

To capture a more robust index of SES that taps into both objective and subjective aspects of socioeconomic position (29), we used a composite score of three z-scored measures of SES: a) yearly family income; b) highest parental education level, coded as a six-level numerical-ordinal variable; and c) parent subjective social status. Each of these scales (described hereinafter) were z-scored and then averaged together. Scale reliability analysis revealed acceptable reliability for the composite items (Cronbach $\alpha = .72$).

Yearly Family Income

Parents were given two options for reporting total yearly family income: a) report exact amount, or if they did not feel comfortable providing an exact amount, b) select from one of nine ranges, as follows: 0$–$5000, $5000–$19,999, $20,000–$34,999, $35,000–$49,999, $50,000–$74,999, $75,000–$99,999, $100,000–$149,999, $150,000–$199,999, and $200,000 and higher. For individuals who reported an income range, we estimated their income as the midpoint of the range. For individuals who selected the income range $200,000 and higher, we recorded their income as $200,000. To increase consistency between methods, all responses were limited to a maximum value of $200,000. Five parents declined to provide income information, which resulted in available income data for $n = 176$.

Highest Parental Education Level

Parents reported on the highest level of education, which culminated in the obtainment of a degree among parents. A six-level ordinal variable was created as follows: 0, less than high school; 1, high school diploma or GED; 2, 2-year or vocational degree; 3, 4-year degree; 4, master's degree; and 5, doctoral level degree. One participating parent declined to provide parental education information, which resulted in available parental education data for $n = 180$.

Subjective Social Status

Parents reported their subjective social status using the MacArthur Scale of Subjective Social Status USA ladder (30). This questionnaire contains two questions asking the participant to rate their subjective social status relative to a) their community and b) their country (the United States) on a scale from 1 to 10, such that higher scores reflect greater relative social standing. Subjective social status data were missing for $n = 12$ participants for the following reasons: participant error (e.g., marked in-between two levels on the ladder; $n = 6$) and declined to provide this information ($n = 6$). This resulted in available subjective social status data for $n = 169$ participants.

Global Health Impairment

Children's global health was measured via parent report, using a five-item subscale from the MacArthur Health and Behavioral Questionnaire for Late-childhood and Adolescence Version 2.1 (31). This subscale contains five items, answered on a 4-point Likert type scale, that address the child's general physical health (e.g., "Would you say your child's physical health is excellent, good, fair, or poor?" "How often in an average month does your child stay home or come home from school because of illness?"). Each item is scaled such that higher scores represent greater health impairment. Items were then averaged together to produce a global health impairment score. This scale has been previously used in an examination of the association between SES and child health (26). In the current sample, this scale exhibited acceptable reliability (Cronbach $\alpha = .68$). Two parents declined to provide global health impairment data, resulting in available data for $n = 179$ participants.

Chronic Health Conditions

Children's number of chronic health conditions was also measured using the MacArthur Health and Behavioral Questionnaire for Late-childhood and Adolescence Version 2.1 (31). Parents were asked to report if their child had ever had any of 21 different chronic health conditions (e.g., asthma, inflammatory bowel disease, chronic ear infections). A final question allowed parents to report other chronic health conditions not included in the list. Because the proposed hypothesis that child parasympathetic activity would moderate the effect of SES on physical health through modulation of physiological and inflammatory reactivity to psychosocial threat, we did not include the following conditions: birth defect, as our hypothesis did not pertain to prenatal effects of SES and fetal PNS activity; and hearing, vision, learning, or speech disorders, as we had no a priori theoretical rationale for examining PNS moderation of SES effects on these disorders. However, robustness checks revealed that results were comparable, and inferences identical, when all disorders were considered. Results from the remaining 17 chronic health conditions were summed up to create a count variable. Two parents declined to provide information on their child's chronic health conditions, resulting in available data for $n = 179$ participants.

Serum Cytokines

Cytokine assays were performed at Northwestern University in the Foundations of Health Research Center using the following procedure: after the serum aliquots had been thawed, they were assayed in triplicate for the following cytokines: interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor α (TNF-α). Assays were performed with a custom four-plex assay on the Simple-Plex Platform (Protein Simple, San Jose, California). This integrated system conducts automated fluorescence immunoassays using disposable microfluidic cartridges. It yields data with high levels of accuracy and reproducibility (32). In the current study, the interassay CVs were as follows: 8.53% for IL-8, 7.01% for IL-10, 6.36% for IL-6, and 5.84% for TNF-α; intra-assay CVs for triplicate runs were as follows: 4.87% for IL-6, 4.73% for TNF-α, 3.33% for IL-10, and 2.36% for IL-8.

Of the 102 participants who provided a serum sample, one participant had an IL-6 value that was deemed abnormally high (>10 SD above the mean) by the laboratory that performed the assays. This value was excluded from analysis. Of the remaining participants, we identified one IL-6 outlier, one IL-8 outlier, and two IL-10 outliers, defined as >3 SD above the mean. These values were Winsorized to the highest value within 3 SD of the mean. IL-6, IL-8, and IL-10 values exhibited positive skew, so a natural log transformation was performed. To obtain an index of general inflammation, we calculated a cytokine composite score similar to prior studies (e.g., Ref. (33)). IL-8 values were not correlated with any other cytokine (p values > .38). In addition, principal component analysis with all four cytokines suggested two components: one with IL-6, IL-10, and TNF-α, and another with IL-8 alone. IL-8 was therefore not included in the composite. Principal component analysis with the remaining three cytokines (IL-6, IL-10, and TNF-α) suggested a single component; these cytokines were therefore standardized and averaged together. The bivariate correlations between the different cytokines and the cytokine composite score were as follows: IL-6 ($r = 0.65$, $p < .001$), IL-10 ($r = 0.78$, $p < .001$), and TNF-α ($r = 0.73$, $p < .001$), suggesting that this composite captured their shared variance well.

Respiratory Sinus Arrhythmia

RSA is a common index of parasympathetic modulation of cardiac activity, which reflects heart rate (HR) variability within the normal patterns of increasing and decreasing HR during inhalation and expiration, respectively (20). RSA (units = $\ln(ms^2)$) was derived from high-frequency power HR variability, obtained using a MindWare ambulatory electrocardiograph (ECG; MindWare, Westerville, Ohio), in accord with recommendations of the Society for Psychophysiological Research committee on HR variability (34). Three silver ECG electrodes, with a 7% chloride wet gel, were attached to the participant's chest and sides in a standard triangle configuration. RSA data were collected during a 5-minute resting period, as part of a larger physiological data collection procedure that involved random assignment to one of three experimental conditions. Current analysis focused on the resting measure, which occurred before experimental manipulation. During the resting period, children remained in a seated position on a comfortable couch, in the company of their parent or guardian. Children were asked to try to relax, to remain seated during the 5-minute duration, and to refrain from talking to their parent or guardian.

Interbeat interval data were calculated using an automated algorithm in the MindWare Biolab acquisition software. A high-frequency band-pass filter set at 0.23 to 0.50 Hz was used to correspond to the average breathing rate of this age range (35). Sampling rate was set at 500 Hz. R-peaks were inspected and cleaned for artifacts by trained researchers using MindWare Heart Rate Variability software. Arrhythmias (e.g., ectopic beats) were corrected using the MindWare midbeat function, which averages the

interbeat interval and minimizes the influence of artifacts. RSA was calculated, using a Fast Fourier transformation algorithm, in 60-second epochs (34). A 60-second epoch was considered usable when it met two criteria: a) at least 30-seconds of continuous, usable data were available, and b) less than 10% of R-peaks were estimated. RSA during the individual 60-second epochs were then averaged together. Resting RSA data were missing for eight participants for the following reasons: technical malfunction (n = 6), participant request (n = 1), and scheduling conflict (n = 1). This resulted in available resting RSA data for n = 173 children.

Statistical Analysis

Statistical analyses were performed using RStudio version 1.3.959. To test the association between SES, health, and inflammation, as well as testing RSA as a moderator of these associations, we conducted a series of linear regressions: a) predicting global health from SES and RSA, b) predicting chronic health conditions from SES and RSA, c) predicting inflammation from SES and RSA, d) predicting global health from inflammation and RSA, and e) predicting chronic health conditions from inflammation and RSA. For each model, we used a stepwise approach: in step 1, we entered the primary independent variable of interest and resting RSA; in step 2, we entered the interaction term between the primary independent variable and RSA; and in step 3, we entered the following covariates: age, sex, and BMI. All variables were mean centered before calculating the interaction term. To control for multiple comparisons, we used the Benjamini-Hochberg false discovery rate (FDR; (36)). For FDR calculations, see Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A815.

The design of this study is cross-sectional, and the term "predicting" is used here to describe associations of these variables with the dependent (outcome) measures in the regression models; the term does not indicate longitudinal associations. For the models predicting global health impairment or inflammation, we conducted multiple linear regressions using ordinary least squares regression. For the models predicting number of chronic health conditions, we used a generalized linear model with a Poisson distribution. A Poisson distribution allows for better modeling of count data, which is integer data characterized by an absence of values below zero and a positive skew (37).

Significant interaction terms were probed using the *interactions* package 1.1.0 in Rstudio (38), which provides both simple slope estimates (significance at the mean, +1 SD, and −1 SD of the moderator) and Johnson-Neyman region of significance estimates (39). A Little's missing completely at random test was not significant ($\chi^2(15) = 21.4$, $p = .12$), consistent with a missing completely at random pattern. Missing data were handled using listwise deletion. However, it should be noted that results were identical when using either full information maximum likelihood or multiple imputations, as described in the Supplemental Digital Content, http://links.lww.com/PSYMED/A815.

Post hoc exploratory analyses, described in Supplemental Digital Content, http://links.lww.com/PSYMED/A815, were conducted to a) explore the relation between parent-child relationship quality and resting RSA, b) investigate racial/ethnic differences in primary study variables, c) test for differential results between subjective and objective measures of SES, and d) test the robustness of our findings after Winsorizing an outlier in global health impairment.

RESULTS

Sample characteristics are presented in Table 1. Complete bivariate correlations are presented in Table 2. As would be expected, global health impairment and number of chronic health conditions were correlated (r = 0.30, $p < .001$). Global health impairment was also positively correlated with inflammation (r = 0.28, p = .004). BMI

TABLE 1. Descriptive Statistics for Total Sample and for Subsample Who Provided Serum Data

	Total Sample (N = 181)		Subsample With Serum Data (n = 103)	
	M or n	SD or %	M or n	SD or %
SES composite	−0.01	0.74	−0.08	0.78
Yearly family income, $	120,603	59,014	120,896	59,953
MacArthur ladder community	6.83	1.42	6.69	1.48
MacArthur ladder country	6.78	1.53	6.72	1.58
Resting RSA	6.32	1.23	6.18	1.27
Global health impairment	0.27	0.34	0.25	0.34
Sum of chronic health conditions	0.49	0.88	0.51	0.87
Age, y	9.91	0.57	9.92	0.58
BMI, kg/m^2	17.72	2.87	17.86	3.10
Sex (female)	89	49.2%	45	43.7%
Highest parental education level				
Less than high school	1	0.6%	1	1.0%
High school or GED	14	7.8%	11	10.7%
2-y or vocational degree	20	11.1%	14	13.6%
4-y degree	63	35%	32	31.1%
Master's degree	54	30%	33	32.0%
Doctoral-level degree	28	15.6%	12	11.7%
Cytokine composite			0.01	0.73
IL-6, pg/ml			1.35	1.32
IL-10, pg/ml			2.48	1.50
TNF-α, pg/ml			6.18	1.36

SD = standard deviation; SES = socioeconomic status; RSA = respiratory sinus arrhythmia; BMI = body mass index; IL-6 = interleukin 6; IL-10 = interleukin 10; TNF-α = tumor necrosis factor α.

TABLE 2. Bivariate Correlations Among Study Variables

	1	2	3	4	5	6	7	8	9	10	11
1. SES	—	−0.01	−0.22**	−0.06	−0.05	0.01	0.07	−0.11	0.18	−0.13	−0.13
2. Resting RSA		—	−0.16*	0.02	0.02	0.09	−0.13	−0.13	0.02	0.05	0.03
3. Global health impairment			—	0.30***	0.28**	0.02	0.05	0.19**	0.01	0.29***	0.20*
4. Sum of chronic health conditions				—	0.11	−0.03	−0.05	0.15*	0.18	0.00	0.02
5. Inflammation composite					—	0.03	−0.08	0.31**	0.65***	0.78***	0.73***
6. Age						—	0.04	0.07	0.03	0.05	−0.01
7. Sex (female = 1)							—	−0.04	0.03	−0.08	−0.15
8. BMI								—	0.34***	0.23*	0.05
9. Interleukin 6									—	0.23*	0.14
10. Interleukin 10										—	0.42***
11. Tumor necrosis factor α											—

SES = socioeconomic status; RSA = respiratory sinus arrhythmia; BMI = body mass index.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

was positively correlated with global health impairment ($r = 0.19$, $p = .010$), number of chronic health conditions ($r = 0.15$, $p = .040$), and inflammation ($r = 0.31$, $p = .002$). Resting RSA was negatively associated with global health impairment ($r = -0.16$, $p = .03$).

SES and Global Health Impairment

Linear regression revealed that RSA moderated the association between SES and child global health impairment, both before and after adjusting for covariates (final model: $B = 0.09$, standard error [SE] = 0.02, $p < .001$; see Table 3 for complete results). Simple slope analysis, presented in Figure 1, revealed that low SES was associated with higher global health impairment for children with low resting RSA (−1 SD; $p < .001$) and mean resting RSA ($p = .012$), but not for children with high resting RSA (+1 SD; $p = .52$). Region of significance analysis revealed that the negative association between SES and global health impairment was only significant for children with resting RSA values less than 6.5 (0.15 SD above the mean).

SES and Chronic Health Conditions

RSA also moderated the association between SES and number of chronic health conditions ($B = 0.27$, SE = 0.10, $p = .005$; see Table S2, Supplemental Digital Content, http://links.lww.com/PSYMED/A815, for complete results). This effect became non-significant after including covariates in the model, as the estimate p value was just above the respective FDR-adjusted α level of α = .03 ($B = 0.22$, SE = 0.10, $p = .031$). For thoroughness, we probed this interaction. Region of significance analysis revealed that lower SES was associated with more chronic health conditions only among children with resting RSA values less than 5.0 (1.08 SD below the mean). For children with resting RSA values greater than 5.0, the association between SES and number of chronic health conditions was not significant.

SES and Inflammation

Linear regression results revealed no main effect of SES on inflammation ($B = -0.06$, $p = .51$). In addition, the SES by RSA interaction was not significant, either before or after including covariates in the model (final model: $B = 0.05$, $p = .47$; Table S3, Supplemental Digital Content, http://links.lww.com/PSYMED/A815).

Inflammation and Global Health Impairment

Linear regression results revealed that RSA moderated the association between inflammation and global health impairment, both before and after adjusting for covariates (final model: $B = -0.12$, SE = 0.03, $p < .001$, see Table 4 for complete results). Simple slope

TABLE 3. Linear Regression Predicting Global Health Impairment From SES ($n = 169$)

	Step 1			Step 2			Step 3		
Predictor	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*
SES	**−0.09**	0.03	.005*	**−0.08**	0.03	0.007*	**−0.08**	0.03	.011*
RSA	−0.03	0.02	.077	−0.04	0.02	.036	−0.03	0.02	.12
SES by RSA				**0.09**	.02	<.001*	**.09**	0.02	<.001*
Age							0.02	0.04	.54
Sex (female)							0.07	0.05	.12
BMI							**0.02**	0.01	.007*

SES = socioeconomic status; SE = standard error; RSA = respiratory sinus arrhythmia; BMI = body mass index.

* Coefficients in bold format whose p values are marked with an asterisk are significant after correcting for multiple comparisons.

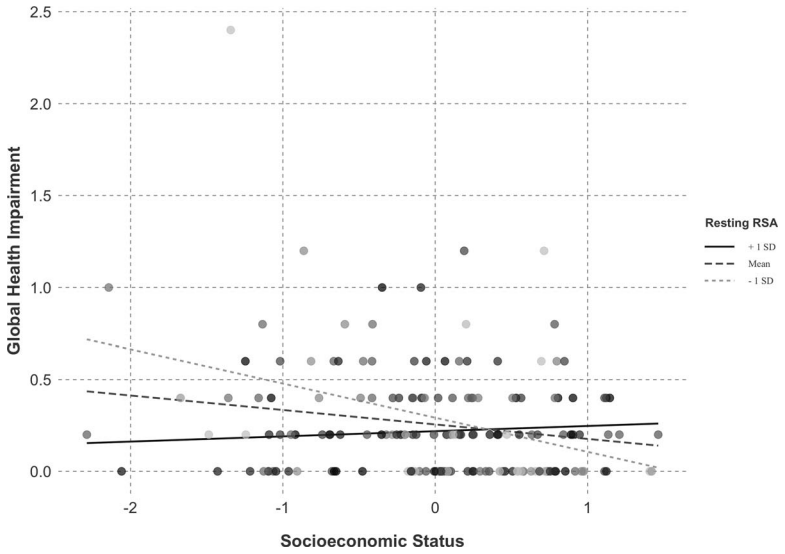

FIGURE 1. Simple slopes representing an association between SES and global health impairment at resting RSA values 1 SD below the mean ($p < .001$), at the mean ($p = .012$), and 1 SD above the mean ($p = .52$), while controlling for child age, sex, and body mass index. RSA = respiratory sinus arrhythmia; SD = standard deviation.

analysis, presented in Figure 2, revealed that higher inflammation was associated with poorer global health for children with low (−1 SD) resting RSA ($p < .001$) and mean resting RSA ($p = .007$), but not for children with high (+1 SD) RSA ($p = .56$). Region of significance analysis revealed that the positive association between inflammation and global health impairment was only significant for children with resting RSA values less than 6.45 (0.11 SD above the mean).

Inflammation and Chronic Health Conditions

Results from the generalized linear model revealed that the association between inflammation and number of chronic health conditions was not significant ($B = 0.23$, $p = .20$). In addition, the interaction between cytokine levels and RSA was not significant either before or after adjusting for covariates (final model: $B = -0.02$, $p = .89$; Table S4, Supplemental Digital Content, http://links.lww.com/PSYMED/A815).

DISCUSSION

Childhood socioeconomic disadvantage is linked to poor somatic health. However, some children who experience socioeconomic adversity exhibit remarkably positive adaptation, indicating resilience (1,14). This study tested resting PNS activity, indexed through resting RSA, as a moderator of the associations between SES, inflammation, and somatic health. We hypothesized that high resting RSA would act as a physiological marker of resilience, such that the associations between SES, inflammation, and somatic health would be weaker for children with high resting RSA. Our findings supported this hypothesis. Specifically, we found that children with lower SES exhibited poorer global health impairment, but that this association was only significant for individuals with low to moderate resting RSA. This is similar to past findings that interparental conflict is linked to poorer somatic health only among children with low resting RSA (25) and, together, suggests that high resting RSA may promote resilience for somatic health in the context of diverse types of adversities.

We also found evidence that resting RSA moderates the association between SES and number of chronic health conditions: lower SES was associated with a greater number of chronic health conditions, but only for children with low resting RSA. These results differ from a previous study of kindergarteners that found that

TABLE 4. Linear Regression Predicting Global Health Impairment From Cytokines ($n = 100$)

	Step 1			Step 2			Step 3		
Predictor	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*
Cytokines	**0.15**	0.04	<.001*	**0.13**	0.04	.002*	**0.10**	0.04	.016*
Resting RSA	−0.05	0.02	.041	−0.04	0.02	.07	−0.03	0.02	.16
Cytokines by RSA			**−0.12**	0.03	<.001*	**−0.12**	0.03	<.001*	
Age							0.03	0.05	.50
Sex (female)							0.03	0.06	.55
BMI							**0.02**	0.01	.021*

SE = standard error; RSA = respiratory sinus arrhythmia; BMI = body mass index.

* Coefficients in bold format whose *p* values are marked with an asterisk are significant after correcting for multiple comparisons.

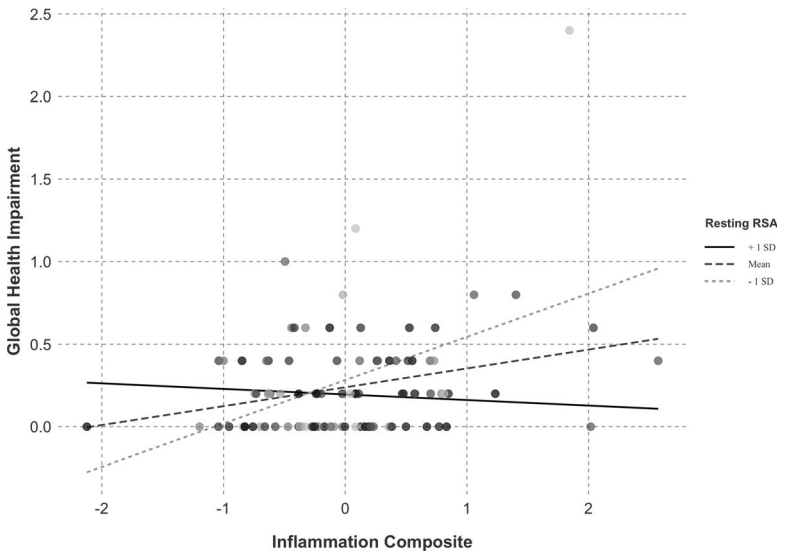

FIGURE 2. Simple slopes representing an association between the inflammation composite and global health impairment at resting RSA values 1 SD below the mean ($p < .001$), at the mean ($p = .007$), and 1 SD above the mean ($p = .56$), while controlling for child age, sex, and body mass index. RSA = respiratory sinus arrhythmia; SD = standard deviation.

RSA reactivity did not moderate the association between SES and chronic health conditions (26), which may reflect differential moderating effects of resting RSA compared with RSA reactivity. Alternatively, this may have resulted from the older age range of our sample. However, considering that these results did not hold up to correction for multiple comparisons, they should be replicated before drawing strong conclusions.

Contrary to our hypothesis, we did not find a significant association between SES and inflammation, and we also found no interaction between SES and resting RSA in association with inflammation. Previous studies have documented associations between SES and inflammation among adolescents (13) and among a very large sample of children (12). Potentially, the effect of early life socioeconomic adversity on inflammation may become more evident in adolescence, either because of latent effects of cumulative exposure to chronic stress or because of a sequential time course of the development of the proinflammatory phenotype (e.g., elevated baseline inflammation may emerge later in life; (40)). Future research should include larger age ranges to test age as a moderator of the association between SES and inflammation.

Prevailing conceptual models link lower SES to poorer health through biological pathways including increased inflammation (41). The current study used cross-sectional data that was not designed for testing mediation. However, these results suggest that, within our sample, the association between SES and somatic health may not be exclusively due to basal systemic inflammation. Alternative mechanisms have been proposed to explain the relation between SES and somatic health, such as health behavior (e.g., exercise, diet) and psychosocial functioning (1). Some evidence suggests that exercise can increase resting RSA (42). In addition, higher RSA has been linked to better psychosocial functioning (27). It is therefore possible that the protective effects of higher resting RSA observed in the current study may be due to higher resting RSA in children engaging in more exercise and having higher-quality social networks. Future multiwave studies should include measures of psychosocial functioning, health behavior, and RSA within a longitudinal design, to investigate the mechanisms involved in socioeconomic disparities in childhood health and further clarify the protective effect of high resting RSA.

Whereas resting RSA did not moderate the association between SES and inflammation, it did moderate the association between inflammation and global health. Specifically, we found that higher inflammation was associated with greater global health impairment, but only among children with low to moderate RSA. Elevated systemic inflammation has been previously associated with poorer self-reported global health in adults (9,10). To our knowledge, this is the first study linking serum cytokines to parent-reported global health in children. The fact that the association between global health and inflammation was not observed among children with high resting RSA suggests that high vagal activity may protect against the deleterious effects of elevated circulating cytokines on somatic health. Consistent with this finding, animal models have experimentally revealed that stimulation of the vagus nerve can dampen cytokine production through the cholinergic anti-inflammatory pathway, leading to better inflammatory-based disease prognosis (21). Considering we did not observe a direct association between resting RSA and inflammation in this study, it is also possible that resting RSA moderated the association between inflammation and global health impairment due to the previously discussed associations between resting RSA and both health behavior and psychosocial functioning. In addition, our sensitivity analysis, described in the Supplemental Digital Content, http://links.lww.com/PSYMED/A815, revealed that the moderating effect of resting RSA on the association between inflammation and global health was attenuated when we Winsorized an outlier (i.e., a child with very poor health). This also suggests our results may be stronger if we had recruited a larger number of children in poor health, covering the full distribution of global health impairment. Because of this, these results should be replicated, preferably within a more diverse sample that includes at-risk children, before drawing strong conclusions.

There was no observed association between cytokines and number of chronic health conditions, suggesting a stronger association between cytokines and parent-reported global health, compared with count of diagnosed health conditions, in childhood. Global health measures reflect subjective appraisals of both diagnosed disease and behavioral manifestations of sickness (10). Parent-reported global health ratings may have been heavily influenced by their child's long-term or recent sickness behavior, which has been extensively linked to inflammation. For example, experimental immune system stimulation has been found to increase sickness behavior (43) and lead to poorer subjective global health ratings (44). Future research should use experimental designs to test resting RSA as a moderator of the effect of immune system stimulation on sickness behavior and global health.

The current study adds novel insight into individual differences in physiology that may underlie risk and resilience in the context of early-life socioeconomic adversity. In addition, to our knowledge, this is the first study to show preliminary evidence that the association between serum cytokine levels and health in childhood may be moderated by resting RSA. However, there are some limitations that should be addressed. First, our results are based on cross-sectional data, which prevents causal or directional inferences. For example, the association between SES and health is likely bidirectional, as caring for a child with health problems can be a substantial financial burden (45). However, alternative directions for the main effects cannot explain the significant interactions with resting RSA. Nevertheless, future research should test these associations and moderation by RSA in longitudinal designs. Our results may also be limited because of the low-risk nature of this community sample, who in general reported relatively good health. Findings may therefore not generalize to more diverse samples that include a larger number of children with poor health. Indeed, the moderating effect of resting RSA on the relation between inflammation and global health impairment seemed to be highly influenced by a single outlier, a participant with a high global health impairment score. Future research could therefore benefit from replicating these findings within a sample that includes higher levels of socioeconomic or other types of adversity. Results from this study may also be limited because of the sample size, which could have been underpowered to detect small effects. Thus, future studies should increase sample size to improve power to detect associations of SES with inflammatory markers.

In addition, because resting RSA was measured with a parent present for all children, our resting measure may reflect the parent's ability to serve as a safety signal. Our exploratory analysis, described in the Supplemental Digital Content, http://links.lww.com/PSYMED/A815, found no association between characteristics of the parent-child relationship and resting RSA. Nevertheless, future studies should replicate our results and consider resting RSA assessed alone versus with the parent to examine their relative predictive utility. Another limitation is that we did not assess parental ANS physiology, which would have allowed us the possibility to test parent-child physiological synchrony and the extent to which this synchrony moderates health outcomes. Another limitation of this study was the use of parent-reported health measures, which may add bias compared with medical records. Furthermore, because we recruited children who agreed to participate in a blood draw, this may limit generalizability if more anxious children declined to participate. Lastly, future research would benefit from collecting information on children's prenatal and postnatal conditions and exposure to early life adverse experiences (e.g., adverse childhood experiences), which could improve our understanding of risk and resilience processes.

In conclusion, we found that lower SES and greater circulating cytokine levels were independently associated with poorer health in children, but that having high resting RSA acted as a protective factor in these associations. Addressing childhood socioeconomic disparities in health remains a significant challenge for modern society. A better understanding of the individual differences that explain why some children who experience economic adversity exhibit poor health, whereas others show resilience, could further refine early risk detection efforts and lead to the discovery of novel intervention methods.

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