Chronic Life Stress, Cardiovascular Reactivity, and Subclinical Cardiovascular Disease in Adolescents

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Objective: To examine cross-sectional and longitudinal relationships between chronic life stress, cardiovascular reactivity, and a marker of subclinical cardiovascular disease in a multiethnic sample of adolescents. **Methods:** Participants were 158 healthy adolescents who completed self-report measures of chronic negative life stress as well as assessments of heart rate and blood pressure reactivity to acute laboratory stressors at two time points, approximately 3.3 years apart. At Time 2, intima-media thickness (IMT), a measure of subclinical atherosclerosis, was also measured. **Results:** In hierarchical regression models adjusting for demographic variables and body mass index, chronic negative life stress at Time 2 was concurrently associated with greater diastolic blood pressure (DBP) reactivity to stress ($\beta = 0.18$, $p = .016$), but neither chronic stress nor cardiovascular reactivity was associated concurrently with IMT. Increasing life stress from Time 1 to Time 2 was accompanied by increasing cardiovascular reactivity ($\beta = 0.14–0.20$, $p < .05$), and increasing DBP reactivity over time was also associated with IMT ($\beta = 0.24$, $p = .03$), although increasing chronic life stress was not directly related to IMT. **Conclusions:** Adolescents exposed to chronic, negative stressors that worsen over time may show heightened cardiovascular reactivity that puts them at risk for subclinical atherosclerosis.
Key words: psychological stress, cardiovascular reactivity, carotid intima media thickness, atherosclerosis, adolescence.

BMI = body mass index; **CVD** = cardiovascular disease; **DBP** = diastolic blood pressure; **ECG** = electrocardiogram; **HR** = heart rate; **IMT** = intima media thickness; **SBP** = systolic blood pressure.

INTRODUCTION

Although cardiovascular disease (CVD) generally manifests in adulthood, its pathogenesis begins in early life, and risk factors in youth predict who will develop subclinical and clinical CVD in adulthood (1–4). Chronic life stress has been identified as a significant risk factor for cardiovascular morbidity and mortality among adults (5), and psychological stress during adolescence may be especially pernicious for cardiovascular health, given that psychosocial and physiological stress response systems develop during this time (6). Thus, adolescence is a critical period in which to examine the relationship between psychological stress and cardiovascular health and a key opportunity for prevention and early intervention efforts. The goal of the current study was to examine relationships between chronic life stress, cardiovascular reactivity to laboratory stressors, and a marker of subclinical atherosclerosis in a sample of healthy adolescents.

Chronic stress early in life demands that developing physiological systems adapt repeatedly to stressful circumstances (7). It has been proposed that exposure to chronic stress leads to repeated, exaggerated cardiovascular responses to acute stressors and that this cardiovascular reactivity may be pathogenic, representing a mechanism by which chronic life stress influences cardiovascular health (8). However, previous research in adults has yielded mixed results with respect to the effects of chronic background stress on cardiovascular reactivity to acute laboratory stressors (9). Few studies have examined the effect of chronic life stress on acute stress responsivity in adolescents, but existing data in youth are also inconsistent. One study reported that important or ongoing chronic stressors were associated with heightened diastolic blood pressure (DBP) reactivity to laboratory stressors (10). Two other studies of adolescents found that cumulative psychosocial stress was associated with blunted cardiovascular reactivity (11,12). This area requires further study.

Chronic stress may also be related to subclinical CVD. Chronic stress has been associated with carotid intima-media thickness (IMT) in adults (13,14), but the relationship between stress and IMT in adolescents has not been examined. Heightened cardiovascular reactivity to acute stress may also have implications for atherosclerosis, as blood pressure reactivity to laboratory stressors has been associated with IMT among adults (15,16) and in a small sample of children (17).

Previous studies of the relationship between chronic stress and cardiovascular reactivity are limited by their cross-sectional design. Although concurrent associations between stress and health are informative, trajectories of persistent or increasing stress exposure over time may be particularly informative when studying individuals who are experiencing rapid changes in CVD risk, i.e., adolescents. Although cardiovascular reactivity is moderately stable in children and adolescents across time in rank order (18,19), the stability of response profiles varies between individuals, and this variation in reactivity parameters may also reflect important individual differences related to stress exposure. The allostatic load model suggests that chronic stress exposure affects cardiovascular health by enacting cumulative wear-and-tear on physiological response systems, which may be reflected in exaggerated cardiovascular reactivity (7). To date, no studies have examined whether persistent or increasing stress exposure is reflected in less salutary physiological reactivity profiles over time and whether individuals who become more reactive over time exhibit evidence of subclinical CVD.

The goals of the current study were to examine both cross-sectional and longitudinal relationships between chronic life stress, cardiovascular reactivity, and carotid IMT in adolescents. With regard to cross-sectional associations, we hypothesized that chronic life stress would be associated with greater

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cardiovascular reactivity to laboratory stress and IMT, and that cardiovascular reactivity would be correlated positively with greater IMT. Longitudinally, we hypothesized that a trajectory of persistent or increasing life stress would predict both increases in cardiovascular reactivity over time and greater IMT, and that increasing cardiovascular reactivity would also predict IMT.

METHODS

Participants

At Time 1 (1999–2002), 213 adolescents aged 14 to 16 years were recruited from two racially and socioeconomically diverse high schools in Pittsburgh, Pennsylvania. Exclusion criteria included congenital heart disorders or a history of cardiovascular or renal disease; use of prescription medications affecting the cardiovascular system; use of recreational drugs; inability to read questionnaires; severe learning disability or mental retardation; documented psychiatric disorder; unwillingness to not smoke for 12 hours before testing; and parental reported weight >80% of ideal for age and gender norms. The University of Pittsburgh Institutional Review Board approved study procedures, and parents/guardians and adolescents provided their informed consent and assent, respectively.

All participants were invited to return for a follow-up assessment an average of 3.3 years (standard deviation = 0.82; range = 1.5–5.9 years) after Time 1, during which assessments of cardiovascular reactivity and chronic life stress were repeated and IMT was measured. The present investigation is based on the 158 participants who participated in the Time 2 laboratory assessment from 2003 to 2005. The most common reasons for not participating in the follow-up assessment were that adolescents could not be located ($n = 29$), they refused ($n = 4$) or relocated ($n = 6$), or there were scheduling problems ($n = 16$). There were no differences at Time 1 in age, race, sex, stressful life events, or cardiovascular reactivity between Time 2 completers and noncompleters.

Procedure

Participants completed a laboratory stress reactivity protocol at Time 1. Electrocardiogram (ECG) electrodes were placed on the chest and neck, and the blood pressure (BP) cuff for auscultatory BP measurement was placed on the nondominant arm. Participants sat in a comfortable lounge chair for calibration of the recording equipment and a 10-minute resting period, during which they were instructed to sit quietly and watch a neutral travel video. At Time 1, this rest period was followed by four stressful tasks (mirror image tracing and mental arithmetic followed by cold pressor and Adolescent Structured Interview) in counterbalanced order with 8-minute resting periods following each task. The stress protocol lasted approximately 50 minutes and was followed by a 10-minute final resting period. After this final rest, participants completed questionnaires.

The procedure was similar at Time 2, except that the adolescents initially had the IMT assessment after completing the informed consent. After this examination, the participants were escorted to the laboratory for stress testing. At Time 2, the initial rest was followed by four stressful tasks presented in counterbalanced order, again with 8-minute resting periods after each task, lasting approximately 50 minutes, and followed by a 10-minute final rest period and questionnaire completion. Due to time constraints, only two of the four tasks (mirror image tracing and mental arithmetic) were identical to those used at Time 1, and reactivity to these tasks is the focus of the present analyses.

Measures

Life Events Questionnaire-Adolescent (LEQ-A)

A modified LEQ-A was administered to participants during each laboratory visit. The LEQ-A was developed to understand the relationship between stressful life experiences and adolescent adjustment (20). During the measure development phase of this scale, expert judges classified each life event on three dimensions including whether the events were (1) negative, positive, or ambiguous (2), dependent or independent of the adolescent's behavior (3) and discrete or chronic in their occurrence. The subscale of interest in the current study was composed of the following five events rated as negative, independent, and chronic: a) there were many arguments between adults living in the house; b) there were many family arguments with relatives; c) a family member developed severe emotional problems; d) a parent had problems at work; and e) the family financial situation was difficult. Adolescents were asked to indicate whether each event had occurred within the past year, and a sum of "yes" responses was created at each time point. In addition to examining concurrent relationships between Time 2 chronic negative life events and cardiovascular health, a summed score to assess persistent life stress (Time 1 + Time 2) as well as a change score to assess increasing life stress (Time 2 − Time 1) were also computed for analyses.

Cardiovascular Reactivity

Two stressful tasks were completed at both time points: mental arithmetic task and the mirror image tracing task. In the mental arithmetic task, an experimenter presented a four-digit number and the participant was asked to count backwards aloud by sevens for 3 minutes as quickly as possible. If the participant got lost, a new number was presented. In the mirror image tracing task, participants were instructed to trace the outline of a figure as rapidly and accurately as possible for 3 minutes while viewing the figure in a mirror. The drawing apparatus is computer-interfaced and provides auditory feedback to the participant when they are tracing outside the boundary of the star shape.

Systolic (SBP) BP and DBP were obtained, using an automated monitor (SD-700A, IBS Corporation, Waltham, Massachusetts). An appropriately sized standard cuff was placed over the brachial artery of the nondominant arm in accordance with published guidelines (21). A trained assistant or nurse, using traditional auscultatory manual BP procedures, validated the placement of the cuff and IBS readings. If the manual readings did not match the IBS readings within 4 mm Hg, the cuff was adjusted and the procedure was repeated until two consecutive matched readings were obtained.

ECG, using three bipolar silver-silver chloride electrodes in a modified lead II configuration on the chest, was transduced to measure heart rate (HR). Two active ClearTrace2 Lt monitoring electrodes were placed on either side of the upper portion of the chest and the ground electrode was placed either on the left upper portion of the back or the left lower portion of the abdomen, below the heart. Ground electrode placement varied for each subject in order to obtain adequate QRS complexes. A high gain bioamplifier with bandpass filter (S75-01, Coulbourn Instruments, Whitehall, Pennsylvania) conditioned the ECG signal.

Carotid IMT

B-mode ultrasound images from the carotid artery were obtained, using a 5.0-MHz linear array transducer and scanner (SSA-270A, Toshiba American Medical Systems, Tustin, California). At Time 2 only, images were obtained from four locations on each of left and right common carotid arteries: near and fall walls of distal common carotid artery, far walls of carotid bulb, and internal carotid artery. Participants were examined in a supine position. Trained readers first scanned the entire circumference of each segment, and the optimal longitudinal view for each segment was captured electronically and stored on magnetic optical disk. The lumen-intima interface and the media-adventitia interface were traced electronically across a 1-cm segment, and the computer generated a measurement for each pixel over this area, using a computerized reading program developed for the Cardiovascular Health Study modified in Pittsburgh. Mean IMT was the average readings across the eight locations. Intraclass correlation among the readings at the eight locations was 0.57. Readings were conducted at the University of Pittsburgh Ultrasound Research Laboratory; raters had no knowledge of the participants' stress or reactivity scores.

Covariates

Adolescents self-reported their age and race/ethnicity, which were subsequently verified with parental interview. Body mass index (BMI) was calculated as weight (kg)/height (m^2) based on measures collected at the follow-up visit. Cigarette smoking within 8 hours of Time 2 IMT assessment and the length between Time 1 and Time 2 assessments were also quantified.

Data Reduction

BP readings were taken at Minutes 5, 7, and 9 of the initial baseline and Minutes 1, 2, and 3 of both stressor tasks. Data for HR were sampled for 55 seconds of each 60-second interval during the last 3 minutes of the initial baseline and during all 3 minutes of each stress task. Reactivity for BP and HR was computed by subtracting the average of the baseline values from the average of the values measured during each task (i.e., task − baseline). At each time point and for each cardiovascular parameter, correlations between reactivity to the two stressors were significantly positive (r = .41–0.67), so a mean reactivity score averaging reactivity to the two tasks was computed for HR, SBP, and DBP at Time 1 and Time 2. Analyses conducted with nonaggregated reactivity scores and with standardized residualized scores yielded similar results.

Statistical Analyses

First, concurrent associations were investigated, using hierarchical linear regression. To examine the effect of chronic life stress on reactivity, BP/HR reactivity from Time 2 was regressed on covariates (Step 1), resting BP/HR at Time 2 (Step 2), and Time 2 chronic life stress (Step 3).[1] Covariates were chosen based on previously documented relationships with reactivity measures and IMT; age, sex, race, and BMI were included as covariates in all analyses (19,22,23). To examine the effect of chronic life stress and cardiovascular reactivity on subclinical cardiovascular disease, IMT was regressed on Time 2 chronic stress and reactivity, adjusting for covariates. Repeated-measures analyses of variance were conducted to determine whether chronic life stress and cardiovascular reactivity changed significantly from Time 1 to Time 2. Next, the predictive utility of persistent or increasing chronic stress and increasing cardiovascular reactivity was examined. Analytical approach was similar to that used to investigate concurrent associations, except that summed or change scores (e.g., Time 1 stress + Time 2 stress, Time 2 reactivity − Time 1 reactivity) were entered as predictors.

RESULTS

Participant Characteristics

Sample characteristics at both time points are presented in Table 1. Repeated-measures analysis of variance revealed that baseline SBP and DBP increased from Time 1 to Time 2 while baseline HR decreased and HR reactivity increased. There was no significant effect of time on self-reported chronic life stress or BP reactivity, and the Pearson correlation between Time 1 and Time 2 reactivity was significant for all three measures of cardiovascular reactivity (r = .43 for SBP; r = .34 for DBP; and r = .50 for HR, after adjustment for baseline BP/HR). The mean of the summed persistent life stress index was 3.43 (standard deviation = 2.54; range = 0–10). Approximately one third (38%) of adolescents in the current sample reported more chronic negative events at Time 2 than at Time 1, i.e., increasing chronic stress, whereas 26% reported the same number of events at the two time points and the remainder reported a decrease. When adolescents with increasing number of chronic stressors were compared with adolescents who reported a stable or decreasing trajectory of chronic stress, there were no significant differences in race, socioeconomic status, or gender ($p > 0.33$).

TABLE 1. Characteristics of Participants at Time 1 and Time 2 (n = 158)

	Time 1	Time 2	Time 2 − Time 1
Age	14.5 (0.61)	17.8 (0.98)	—
% Black	50.2	50.0	—
% Female	50.7	48.7	—
% Smoker	—	13	
Chronic life stress	1.71 (1.64)	1.73 (1.49)	0.00 (1.83)
SBP			
Baseline	104.81 (9.56)	108.24 (8.88)	3.48 (8.89)[a]
Reactivity score	9.07 (7.40)	9.98 (7.66)	0.97 (8.60)
DBP			
Baseline	61.61 (8.96)	63.30 (8.51)	1.72 (9.28)[a]
Reactivity score	9.38 (6.58)	8.45 (6.26)	−1.08 (7.98)
HR			
Baseline	71.42 (9.40)	68.87 (9.84)	−2.75 (8.38)[a]
Reactivity score	3.94 (5.65)	5.91 (4.71)	1.94 (5.31)[a]
IMT	n.a.	0.54 (0.04)	—

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; IMT = intima-media thickness.
Data are represented as mean (standard deviation), unless otherwise indicated.
[a] Effect of time significant at $p < .05$.

TABLE 2. Linear Regression Analyses Relating Concurrent Chronic Stress, DBP Reactivity, and IMT

	DBP Reactivity at Time 2		IMT at Time 2	
	β	p	β	p
Covariates				
Time 2 age	0.08	.30	0.00	.99
Race	0.05	.53	0.17	.04
Sex	−0.18	.02	−0.08	.32
Time 2 BMI	−0.17	.03	0.04	.60
Time 2 smoking status	0.05	.54	0.05	.55
Time 2 baseline DBP	−0.27	<.001	−0.07	.46
Chronic stress at Time 2	0.18	.02	0.02	.80
DBP reactivity at Time 2	—	—	0.14	.12

DBP = diastolic blood pressure; IMT = intima-media thickness; BMI = body mass index.

Concurrent Associations Among Stress, Reactivity, and IMT at Time 2

In models adjusted for race, sex, and Time 2 age, smoking, and BMI as well as resting DBP, chronic life stress was associated positively with DBP reactivity (Table 2). There were no significant relationships between chronic negative life stress and SBP or HR reactivity. In addition, there was no significant association between chronic life stress and IMT.

After adjusting for covariates, greater DBP reactivity was marginally associated with IMT (β = 0.14, p = .10), a trend that was reduced to statistical nonsignificance after controlling for chronic life stress (Table 2). No significant relationships between HR or SBP reactivity and IMT emerged.

[1]We also examined concurrent associations between chronic life stress and cardiovascular reactivity at Time 1. No significant relationships were observed.

TABLE 3. Linear Regression Analyses Relating Increasing Chronic Stress, DBP Reactivity, and IMT

	DBP Reactivity at Time 2		IMT at Time 2	
	β	p	β	p
Covariates				
Time 2 age	0.11	.38	0.03	.85
Race	0.04	.56	0.18	.03
Sex	−0.14	.07	−0.08	.35
Time 2 BMI	−0.11	.19	0.02	.82
Time 2 smoking status	0.09	.28	0.02	.80
Time to follow-up	−0.08	.53	0.00	.99
Time 2 baseline DBP	−0.24	<.001	−0.08	.33
Time 1 DBP reactivity	0.10	.23	0.12	.35
Increasing chronic stress	0.20	.01	−0.02	.85
Increasing DBP reactivity	—	—	0.26	.04

DBP = diastolic blood pressure; IMT = intima-media thickness; BMI = body mass index.

Persistent Life Stress and Cardiovascular Variables

After adjusting for covariates, the summed index of persistent life stress across Time 1 and Time 2 was not significantly predictive of any Time 2 reactivity parameter or IMT.

Increasing Life Stress and Cardiovascular Variables

In regression models adjusted for covariates, baseline BP/HR at Time 2, and reactivity at Time 1, self-reported increases in chronic life stress from Time 1 to Time 2 predicted increases in cardiovascular reactivity including SBP ($\beta = 0.17$, $p = .02$, $\Delta R^2 = .03$), DBP ($\beta = 0.20$, $p = .01$, $\Delta R^2 = .04$), and HR reactivity ($\beta = 0.14$, $p = .05$, $\Delta R^2 = .02$). There was no significant effect of increasing life stress on IMT.

Increases in DBP reactivity from Time 1 to Time 2 were associated with greater IMT ($\beta = 0.24$, $p = .04$, $\Delta R^2 = .03$). This effect remained significant when controlling for increases in stressful life events (Table 3). Changes in SBP and HR reactivity were not significantly associated with IMT.

DISCUSSION

The current study examined both cross-sectional and longitudinal associations between chronic life stress, cardiovascular reactivity to acute laboratory stressors, and carotid IMT in a sample of healthy adolescents. Consistent with previous cross-sectional research (10,12), chronic life stress was associated with heightened DBP responses to laboratory stress. Contrary to hypotheses, a trajectory of persistent negative life stress over time was not significantly associated with reactivity parameters. This may reflect a process of biological and psychological adaptation if exposure to stable, ongoing stressors facilitates the development of coping resources and skills. However, a trajectory of increasing life stress over approximately 3.3 years was accompanied by increases in cardiovascular reactivity to standardized laboratory stressors. This suggests that exposure to increasing levels of negative life stress may be reflected in unhealthy changes in physiological stress response profiles, consistent with an allostatic load model of cumulative stress resulting in physiological dysregulation (7). Future research should examine alternative forms of allostatic dysregulation, such as delayed physiological recovery post stress or failure to habituate to repeated stressors.

In the current study, increasing DBP reactivity over the course of the study was associated with greater IMT. Mean carotid IMT is widely accepted as a noninvasive marker of subclinical atherosclerosis. It correlates strongly with established cardiovascular risk factors (23,24) and with indices of coronary atherosclerosis (25) and predicts future vascular events (26). In the current study, each 1 mm Hg increase in DBP reactivity averaged across tasks from Time 1 to Time 2 was associated with 0.001 mm greater IMT. Although the clinical significance of a relationship of this magnitude remains unclear, a trajectory of increasing stress reactivity that begins in adolescence may be a significant risk factor for accumulating allostatic burden and atherosclerosis and vascular stiffness over the life course.

Associations between SBP reactivity and IMT have been previously reported (17,27), but our findings did not confirm this relationship. However, the association between SBP reactivity and IMT in adults became nonsignificant after adjustment for standard risk factors (e.g., lipids, glucose, and insulin) whereas the association between DBP reactivity and IMT remained significant in some (15) but not all reports (27). We also found no relationship between HR reactivity and IMT, consistent with prior reports (15,17,27). One proposed mechanism underlying the BP reactivity and IMT association is that pressor-induced disruptions to blood flow result in endothelial injury (28), a model consistent with the finding that HR reactivity does not predict IMT.

Although chronic stress was related to heightened reactivity and heightened cardiovascular reactivity was related to IMT, we found no evidence of a direct relationship between chronic life stress indices and IMT. Perhaps the effects of chronic stress on IMT emerge only later in life, after individuals have more time to accumulate atherosclerotic plaque. Stress exposure may also predict IMT only for vulnerable individuals, such as those with fewer coping resources.

A major limitation of the current study is the single assessment of IMT, which limits inferences that can be made about the progression of atherosclerosis over time. Another limitation was the brief assessment of chronic life stress, which may not have comprehensively captured the chronic life stressors faced by adolescents and did not include severity or duration of stress exposure. A more thorough examination of life stress may have yielded larger effects and greater consistency across outcomes. The sample was also healthy, with restricted range for IMT, and may not be representative of adolescents most at risk for cardiovascular morbidity.

Strengths of the study include repeated assessments of stressful life events and cardiovascular reactivity to standardized laboratory stress, the diverse adolescent sample, and inclusion of a validated measure of early vascular thickening.

In summary, chronic life stress during adolescence is associated with heightened DBP reactivity to acute stress. A trajectory of increasing chronic stress during late adolescence was reflected in increasing magnitude of cardiovascular stress responses over time, and increasing DBP reactivity was predictive of IMT. Thus, adolescents exposed to chronic, negative, uncontrollable life stressors, especially stressors that worsen or increase over time, and those that are physiologically reactive to acute stressors represent important targets for early interventions. Future research should examine the role of healthy coping strategies (e.g., exercise) and resources (e.g., social support) in buffering the effects of stress on health, as identifying such moderators could aid the development of early intervention and prevention efforts.

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