HHS Public Access

Author manuscript

Stress. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Stress. 2016 May ; 19(3): 269–279. doi:10.1080/10253890.2016.1174847.

Cumulative stress and autonomic dysregulation in a community sample

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Abstract

Whether cumulative stress, including both chronic stress and adverse life events, is associated with decreased heart rate variability (HRV), a non-invasive measure of autonomic status which predicts poor cardiovascular outcomes, is unknown. Healthy community dwelling volunteers, (N= 157, mean age 29 years) participated in the Cumulative Stress/Adversity Interview, (CAI) a 140-item event interview measuring cumulative adversity including major life events, life trauma, recent life events and chronic stressors, and underwent 24 hour ambulatory ECG monitoring. HRV was analyzed in the frequency domain and standard deviation of NN intervals (SDNN) calculated. Initial simple regression analyses revealed that total cumulative stress score, chronic stressors, and cumulative adverse life events (CALE) were all inversely associated with ultra low frequency (ULF), very low frequency (VLF), and low frequency (LF) power and SDNN (all $p<0.05$). In hierarchical regression analyses, total cumulative stress and chronic stress each was significantly associated with SDNN and ULF even after the high significant contribution of age and sex, with no other covariates accounting for additional appreciable variance. For VLF and LF, both total cumulative stress and chronic stress significantly contributed to the variance were no longer significant after adjusting for race and health behaviors. (p's<.05). In summary, total cumulative stress, and its components of adverse life events and chronic stress were associated with decreased cardiac autonomic function as measured by HRV. Findings suggest one potential mechanism by which stress may exert adverse effects on mortality in healthy individuals. Primary preventive strategies including stress management may prove beneficial.

Keywords

Heart rate variability; autonomic nervous system; stress; adversity

Introduction

The role of stress in contributing to overall and cardiovascular mortality is well-described. Many ongoing or recent stressors, such as work stress (1) (2), caring for a sick spouse (3), or

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Declaration of Interests: The authors have no competing interests to report.

bereavement (4), and prior stressors, such as childhood adverse experience (5–7), lead to increased incidences of cardiac disease and worsened survival. Cumulative stress, that is, repeated stressors occurring throughout the lifespan, may be as or more important than single specific stressors (8). For example, while socioeconomic adversity either currently or in the past is a risk factor for cardiovascular disease, the cumulative impact of sustained economic hardship leads to greater cardiovascular as well as total mortality than does economic hardship at any one time (9, 10).

Cumulative stress, representative of lifetime exposure to adversity, is thought to exert its influence through a “chain of risk,” wherein early adverse life events exposure increases risk for later exposures in an ongoing positive-feedback loop (11, 12). This cumulative stress in turn impacts physical, mental and behavioral outcomes (13, 14). For example, cumulative stress over the lifetime increases prevalence of hypertension, physical disability, pain and other chronic diseases as well as psychiatric disorders, alcohol, and drug abuse (11, 12, 15–19).

Physiological pathways linking cumulative stress to physical disease have not yet been elucidated. Specific stressors such as chronic work stress (20) and lower socioeconomic status (21, 22) may work to impact clinical outcomes through adverse effects on autonomic nervous system (ANS) function. ANS function can be non-invasively measured by methods of heart rate variability (HRV) analysis, which quantifies the beat-to-beat changes in heart rate caused by changes in sympathetic and vagal activity (23, 24). Depressed HRV is associated with increased vulnerability to cardiac events, correlating with increased mortality in the general population (25, 26) as well as poor prognosis after myocardial infarction (27, 28). Whether cumulative stress might similarly adversely impact autonomic physiology in otherwise healthy community samples has not been previously explored.

Thus, the primary goal of this study was to determine whether cumulative stress may impact HRV, and to what extent such an association may be influenced by selected demographic, behavioral, or psychological factors. We collected ambulatory ECG data for HRV and data on cumulative stress in a community cohort of healthy individuals with no current psychiatric or physical disease, and also assessed demographic and behavioral risk factors such as smoking BMI and alcohol use as well as age, race and sex, factors known to decrease HRV (29).

There are a number of methodologies which can be used to quantify HRV (30). We chose to measure a panel of frequency-domain variables and standard deviation of NN intervals SDNN over 24 hours, as many of these have been strongly associated with psychosocial characteristics (21, 31, 32), and health outcomes (28, 33). There are data suggesting that each of the HRV parameters evaluated in this study may reflect alterations in cardiac autonomic modulation. High frequency (HF) power is well-established as a marker of parasympathetic activity (23, 24), although 24-hour recording is limited by non-stationarity and HF may be less reliable over 24 hours (30). Early data suggested that low frequency (LF) might be a marker of sympathetic activity (24). However, this is highly controversial. The limitations of these data have been extensively discussed (34) and recent experimental data shows no correlation between LF and directly-measured cardiac sympathetic activity

(35). Some (36), although not all (35), data suggest that LF may instead reflect baroreceptor sensitivity, a marker of autonomic control of circulation which is predominantly vagally mediated (37). Different studies have found very low frequency (VLF) to reflect thermoregulation or activity of the renin-angiotensin system (38) or predominantly parasympathetic activity (39). The physiological underpinnings of SDNN and ultra low frequency (ULF) are less well-understood. SDNN, measuring total variance over 24 hours, is associated with baroreflex sensitivity (40). Both SDNN, reflecting all variance, and ULF, reflecting variance below .0033Hz, reflect circadian variation, which is autonomically controlled (33). ULF also reflects non-harmonic variations in heart rate, such as those due to physical activity (41). Physical activity has not been found to influence SDNN (40).

Cumulative stress was measured using the cumulative stress/adversity interview (CAI) (11, 12, 15–17, 42–44) which provides data on a series of cumulative major life events, life traumas, recent life events and chronic stress. This instrument captures both a composite lifetime measure of exposure to cumulative adverse life events (CALE) (major and recent life events and traumatic life events) and a measure of chronic stress which captures ongoing stressors perceived by the subject to be overwhelming and challenging, thus creating also a total cumulative adversity/stress (Total CAI) measure which combines external stressors with subjective perception of stress. We hypothesized that high cumulative stress will be associated with lower HRV, and that this association will remain significant after controlling for any significant demographic and behavioral health risk measures in a community sample.

Methods

Study participants

One-hundred and eighty-seven participants without known cardiovascular, psychiatric or other medical diseases and taking no medications were recruited from a community sample in and around the New Haven area via advertisements placed either on-line or in local newspapers and community centers. Eligibility was ascertained via an initial phone screen. All participants were between the ages of 18 and 50 years and able to read and write in English to at least a 6^{th} grade level. All met stringent health requirements assessed by a specialist research nurse. This project was designed to study a young to middle age healthy sample and hence we selected the 18–50 age range. Exclusion criteria included DSM-IV-TR (45) dependence for any drug other than nicotine, any cardiovascular, renal, endocrine, neurologic and immune medical disorders, any psychiatric disorder by history, mood or anxiety disorder as measured by the Structured Clinical Interview for the Diagnostic and Statistical Manual (SCID-IV-TR (46)) and use of prescribed medications for any psychiatric or medical disorders. All individuals underwent physical health exam and laboratory testing to rule out abnormal renal, cardiac, hepatic, pancreatic, and hematopoietic and thyroid function. All participants gave written informed consent and the study was approved by the Human Investigation Committee of the Yale University School of Medicine.

Potential subjects completed an initial screening over the telephone to determine eligibility based on inclusion/exclusion criteria. Following initial eligibility screening, the participants were scheduled for an intake evaluation, a physical health exam (including BMI, treated as a health behavior by the American Heart Association (47) as well as many risk-factor

investigators (48)) and laboratory testing. They underwent an additional assessment session to prospectively assess cumulative stress , physical and psychiatric health and assessments on alcohol use, and cigarette smoking. They also completed psychological assessments on mood, anxiety, emotion regulation and impulsivity to assess individual psychological characteristics. During all assessment sessions, participants underwent breath alcohol and cotinine testing and urine toxicology screens in order to confirm freedom from alcohol and illicit drugs. The 24-hour HRV monitoring was obtained within 1–2 weeks following the third assessment session.

Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Axis 1, Fourth Edition, Research Version (SCID)—The SCID was utilized to determine current and lifetime psychiatric disorders (45). This is a widely-used and well-validated clinical interview based on the DSM-IV (49) with updates for the DSM-IV-TR (45). The interview was administered by clinical research associates who had completed SCID-IV training using SCID-IV training tapes and under the supervision of a licensed clinical psychologist (Dr. Keri Tuit) with extensive experience performing structured diagnostic evaluations, and specifically with extensive experience administering the SCID with different community samples.

The Cumulative Stress/Adversity Interview: (CAI, based on Turner and Wheaton, 1995)(42)

The CAI, based on the Turner & Wheaton model of cumulative stress and adversity (50) is a comprehensive 140-item interview encompassing a multifaceted assessment of stressful life events and chronic, subjective stress previously used in prospective, longitudinal research on stress and psychopathology and found to be highly predictive of psychiatric disorders over the lifetime (44). The measure was administered in a structured interview format by trained interviewers supervised by a licensed clinical psychologist (KT). Trained interviewers ask participants about the occurrence and frequency of specific Major Life Events, Recent Life Events, Life Trauma and Chronic stress during their lifetime. Prior research supports the use of interviewers to efficiently improve reliability and validity of retrospective reports of stressful life events (51).

The CAI includes four subscales, one for Chronic Stress, and three subscales for cumulative adverse life events (CALE), which include: a) Recent Life Events, b) Major Life Events, and c) Life Traumas. The 33-item Recent Life Events subscale assesses stressful events which occurred in the previous 12 months. Events are broadly divided into items referring to social losses (e.g., death, divorce, relationships ending), undesirable interpersonal and financial events (e.g., being attacked, financial crises, and robberies) and work-related experiences (e.g., being laid off, demotion, going on strike). The 11-item Major Life Events subscale includes 11 items relating to past social adversities prior to the recent 12 month period, not typically violent in nature, but which differ from standard life events due to their severity and potentially long-term consequences (11). Examples of items are parental divorce, failing a grade in school, and losing a child. The 34-item Life Trauma subscale consists of 34 items relating to past traumatic events, witnessed violence and traumatic news. Such events may include physical, emotional and/or sexual abuse, such as rape or being injured with a weapon. Witnessed violence may involve being present in dangerous or upsetting situations,

such as seeing someone get shot or attacked with a weapon. Traumatic news is comprised of items which involve not being present, but rather hearing news about someone else being killed, abused or injured. Finally, the Chronic Stress subscale comprises 62 items relating to subjective experience of being overwhelmed and challenged by ongoing stressors and adverse life events included in the above life events scale. Subjective response to continuous stressors or ongoing life problems are scored on a three point Likert-type scale ranging from not true to very true and refer to perceived difficulties with ongoing interpersonal, social and financial relationships and responsibilities including difficulties in the work and home environment and relationships with family and significant others.

Using responses to the three life events subscales, a Cumulative Adverse Live Events (CALE) score was computed by first, standardizing each life exposure subscale (z-transform in comparison to the full sample), and second, summing the resulting three z-scores for the CALE score. This approach ensured that each category of events was weighted equally in the final score. In all cases, a higher score relates to a higher number of stressful events. The total raw score of the 62 items making up the chronic stress subscale was also standardized into a z score. Finally, a total cumulative stress z score was computed which combined the CALE and the chronic stress z scores.

Reliability of the CAI subscales and CALE is good. In the current sample, the intra-class correlations (ICCs) for the 157 subjects were 0.81 for the Chronic stress, 0.83 for the CALE scores and 0.83 for the Total cumulative stress cores. In addition, the month test-retest reliability was computed for the current sample of participants in the study (n=157). Reliability coefficients for major life events (MLE), lifetime traumas (LT), recent life events (RLE), cumulative adverse life events (CALE combining MLE, LT and RLE), and chronic stress were .90, .88, .73, .88, and .82 with an overall CAI reliability coefficient of 0.86, indicating good to excellent reliability across scales. These reliabilities are also consistent with, test-retest coefficients reported by our group in previous work using the CAI (52, 53).

Table 1 presents the demographic and behavioral risk data as well as total cumulative stress score (combined CALE and Chronic Stress), CALE alone and Chronic Stress alone, based on standardized z scores.

Processing of Holter recordings and HRV analysis

Ambulatory ECGs were recorded over 24 hours on GE Seer and Seer Lite recorders (digital sampling 125 sps). Recordings were scanned using a GE Mars Ambulatory ECG system (PC, version 7). Each tape was manually processed and edited. A list of R-R intervals with annotations denoting normal beats, types of ectopics, and noise was generated by the GE program and was transferred to a separate workstation where it was processed and analyzed with customized software replicating methods described in the literature (54). The RR interval data file was edited to remove ectopics and noise, and gaps filled in by interpolated linear splines. The power spectrum was computed using a fast Fourier transform with a Parzen window and corrected for attenuation due to windowing and sampling. The power spectrum was integrated over five discrete frequency bands as defined by Bigger et al (28): ultra low frequency (ULF) < 0.0033 Hz; very low frequency (VLF) 0.0033 to < 0.04 Hz; low frequency (LF) 0.04 to < 0.15 Hz; and high frequency (HF) 0.15 to 0.40 Hz. The standard

deviation of NN intervals (SDNN) was computed. Mean duration of analyzed data was 21.2 hours (SD=5.6) with mean 1.7% (SD=3.2%) interpolated. Individuals with holters with >20% interpolated QRS complexes were excluded, N=30.

Statistical analysis

The remaining 157 subjects comprise the study group. All HRV parameters except SDNN were highly skewed and therefore natural log transformed. Analyses of Variance (ANOVAs) were performed for categorical variables to assess their predictive effects on HRV parameters, including sex, smoking status, education and race and using simple linear regression for continuous predictors such as BMI, number of days of alcohol used in the past month and the total cumulative stress as well as the CALE and chronic stress measures separately (Table 2 and 3). To evaluate the association of each stress measure with HRV, and the additional contribution of demographic and behavioral risk variables such as age, sex and race, BMI and smoking status, significant demographic and behavioral variables known to be associated with HRV (29), we conducted hierarchical regression analyses. As recommended by Tabachnick and Fidell (55), we used hierarchical regression analyses because we had *apriori* hypotheses that stress will be associated with HRV, and thus, stress was given priority and entered first in the hierarchical model. This was followed by the addition of known demographic and behavioral risk contributors to HRV to assess change in stress effects on HRV with the addition of these known factors. Hierarchical regression analyses were conducted separately for each stress measure and not jointly in the same set of regressions to protect against multicollinearity risk (55). For each HRV measure, the specific stress measure was entered in Block 1 to assess its contribution to the variance in HRV response. This was followed by the addition of age in Block 2, and sex in Block 3, with a final Block 4 including race, BMI and smoking status.

Because sex was strongly associated with HRV measures, post-hoc, a sex by stress interaction term was included in secondary hierarchical regression analyses.

Results

Study participants

As shown in Table 1, the 157 participants included in the analysis had a mean age of 29 years and 55% were male. Participants were free of known cardiovascular, psychiatric and other renal, endocrine, neurologic or immune diseases and were taking no medications as specified by the inclusion criteria. Demographic and behavioral characteristics of the cohort, as well as mean stress scores are shown in Table 1. Two-thirds were Caucasian and most had completed high school.

Relationships among Demographic and Behavioral Risk Factors, and Stress Indices and HRV

As shown in Table 2, sex was highly significantly associated with each HRV measure with the exception of lnHF, with women showing lower HRV compared to men (p's <.001). Individuals of Caucasian race had significantly higher HRV for all measures except HF. Smoking and higher BMI were associated with lower HRV for most measures. Education

and number of days of alcohol use in past month did not significantly predict HRV measures (Table 2). Thus education and days of alcohol use in the past month were not included in the final hierarchical regression models. Higher CAI total cumulative stress scores, as well as the CALE and Chronic Stress measures were each separately associated with lower values for all HRV indices except HF (Table 3). As expected, the combined CAI total score was highly correlated with CALE ($r=0.94$, $p<.0001$) and moderately but significantly correlated with Chronic Stress ($r=0.68$, $p<.0001$) and CALE and Chronic Stress were modestly but significantly correlated with each other ($r=0.39$, $p<.0001$) in the current sample.

Multivariate Hierarchical Regression Analyses for each Stress Measure with HRV Variables, and including Demographic and Behavioral Variables

As shown in Table 4, for SDNN, total cumulative stress ($p<.0001$) and chronic stress ($p<.0001$) each accounted for 5% of the variance, while CALE ($p<.01$) accounted for 3% of the variance in SDNN alone, in separate models. Both age and sex contributed significantly to the variance in SDNN, and stress measures remained significant in the model with these additions. The addition of race, BMI and smoking to the model did not contribute significantly to the variance in SDNN for any of the stress variables.

As shown in Table 5, for ULF, each of the stressors alone contributed similarly to ULF variance. With the addition of all covariates, in the final models, both CAI total stress and Chronic Stress remained significantly associated but CALE did not.

Findings for VLF and LF are shown in Tables 6 and 7. For each of these HRV variables, each stressor contributed similarly to the variance alone, and remained significantly associated with HRV after addition of age and sex to the model. However, with addition of race, and behavioral variables BMI and smoking, none of the stressors remained significant.

The stress measures did not contribute significantly to the variance in HF on their own or with the addition of demographic and behavioral health variables (data not shown).

Sex, Stress, and HRV

As shown in Table 1, all stress measures were higher in women than men. HRV measures were all lower in women. In secondary analyses, entering of an interaction term between sex and stress in the hierarchical regression analysis revealed there was no significant interaction between sex and stress for any of the HRV measures.

Discussion

In this study, all HRV parameters were lower in individuals with higher total cumulative stress as measured by the CAI as well in those with a greater amount of chronic stress as measured by the Chronic Stress subscale and with higher numbers of adverse life events (CALE). Results of the hierarchical regression analyses indicated that total cumulative stress as measured by the CAI total score, chronic stress as measured by the Chronic Stress subscale, and CALE each were significant in accounting for a small amount of the variance in each of the measures. Both CAI total score and Chronic Stress (subscale) remained significantly associated with SDNN and ULF after inclusion of demographic and behavioral

risk variables in the model. For VLF and LF, however, associations with stress scales were no longer significant after adding race, BMI and smoking to the models.

Physiologic studies have demonstrated that most HRV variables reflect the effect on the sinus node of modulations of autonomic tone (23, 24). While the cross-sectional nature of this study does not allow definitive determination of causality, the consistent lower values of HRV shown here suggests that total cumulative stress, with its components of chronic stress and cumulative adverse life events, may contribute to a state of cardiac ANS dysfunction, independent of any existent mental or physical disease state. While prior studies have shown the effects of single specific stressors on HRV, including work stress, anxiety, low socioeconomic status, and depression (20, 21, 31, 56–58), this is the first to show that cumulative stress over the lifespan, as measured by the CAI total score, is associated with reduced HRV.

As described in the introduction, many of the HRV indices associated with stress in this study reflect autonomic function. For example, SDNN and LF are influenced by baroreflex function (36, 40), a measure of parasympathetic function, and VLF has also been associated directly with parasympathetic function (39). Our data thus suggest stress to be associated with reduced parasympathetic activity. ULF and SDNN have been associated with circadian variation, and also more broadly associated with autonomic function, suggesting stress may be associated with abnormalities in circadian variation. Physical activity could be another mechanism linking stress and HRV. Negative emotion may decrease physical activity (59). As ULF is influenced by activity (41), it is possible that stress-related differences in physical activity may underlie differences in ULF. However, SDNN has not been shown to be influenced by activity (40), suggesting that activity is not the primary driver of the overall findings.

Based on the current data, one may speculate on potential mechanisms by which cumulative stress over the lifespan may relate to poor cardiovascular outcomes and increased mortality, a well-documented clinical finding (1, 3–8). Lower indices of HRV predict morbidity (25) and mortality (25, 26) in normal individuals, as well as patients after myocardial infarction (27, 28). Altered cardiac ANS function may directly contribute to cardiac mortality, as sympathetic hyperactivity and decreased vagal tone increase cardiac workload, predispose to arrhythmia (60, 61) and alter endothelial function (62), enhancing atherosclerosis. Or, HRV may be a more general indicator of autonomic function, impacting broadly on health status and outcomes. Changes in autonomic function may thus be physiologic mediators of the effects of cumulative stress on cardiovascular outcomes, a hypothesis that would need specific testing in future studies.

How cumulative life stress might affect cardiac autonomic function is not known. Stress influence health behaviors such as smoking, BMI (as a proxy for poor eating habits) and alcohol use (63), and these factors also influence autonomic function, as shown in prior studies (29, 64, 65). In our study, the relationship between stress and VLF and LF HRV may have been mediated by these health behaviors, as inclusion of BMI and smoking led to the stress measures falling out of significance. However, the associations of total and chronic stress with SDNN and ULF remained significant even after addition of behavioral risk

factors to the model. These results are consistent with prior studies that show life stressors impact cardiovascular morbidity and mortality independent of alterations in health-related behaviors. For example, in the Adverse Childhood Experiences Study ("ACES"), the increased heart disease seen in individuals exposed to early adverse experiences was attenuated very minimally after controlling for behavioral factors including smoking, BMI, and physical activity (48).

How stress may directly impact HRV is unknown, but it may be related to its effects on central pathways involved in regulating autonomic function. There is significant basic science and clinical research showing dysfunction of brain emotional arousal and prefrontal regulatory pathways with stress exposure (66, 67). Cumulative stress is associated with smaller gray matter volume in key regions of the brain involved in emotional, social, and self-regulation, as well as top-down control of limbic and reward-focused processes in young community-dwelling adults (52). Furthermore, these effects of cumulative stress were mediated by levels of chronic stress (52), suggesting that chronicity of stress is critical to the stress-related gray matter volume reductions in these key regions. Thus, while speculative, it is possible that cumulative stress, and especially chronic stress, modifies these corticolimbic circuits that play a role in modulating autonomic arousal during challenge, thereby resulting in heightened sympathetic arousal in response to stress throughout the life course which may over time lead to chronic dysregulation of autonomic function (61). Additionally, stress could also impact circadian variation, underlying ULF and SDNN, through impact on sleep or other mechanisms.

The impact of total cumulative stress on autonomic function is consistent with the allostatic load model. The ability of physiologic systems to adapt to stressors, or "achieve stability through change," has been described as "allostasis"(68). According to the allostasis paradigm, as discussed by McEwen and others, "health functioning requires ongoing adjustments of internal physiologic milieu, with physiologic systems exhibiting fluctuating levels of activity as they respond and adapt to environmental demands" (68). Repeated stressors over the lifetime can increase allostatic load and result in "wear and tear of the regulatory systems" which has been shown to correlate with increased mortality (68). It has been suggested that HRV may provide an integrated measure of allostasis (69). Thus, the lower HRV seen in individuals with heightened exposure to both cumulative adverse life events and chronic stress as measured in this study may reflect increased allostatic load, resulting in this "wear and tear," thereby dampening cardiac autonomic regulatory functions and increasing vulnerability to disease. It is important to note that total cumulative stress, (CAI) a combination of life events and the person's response to the events (i.e., subjective sense of feeling overwhelmed and challenged chronically), was more closely associated with HRV than life events (CALE) alone. This finding underscores the importance of the chronic stress in adversely affecting health outcomes.

The impact of chronic stress on autonomic function is also consistent with allostatic load models where exposure to repeated stress increases maladaptive cognitive and behavioral coping, that in turn, decreases an individual's ability to reduce physiological, sympathetic arousal via adaptive coping (70). Thus, chronic stress is a well-established risk factor for stress-related psychiatric illnesses such as major depression, in turn associated with reduced

HRV parameters. However, in this study, chronic stress as measured by the Chronic Stress subscale was directly associated with decreased HRV even without the presence of depression as in the current healthy sample.

In this study, women showed lower levels of HRV for all variables except HF, and African-Americans (19% of the sample) significantly lower levels for VLF and LF, with borderline differences for SDNN and ULF. Numbers of Hispanic and Asian subjects were too small for meaningful analysis. Prior data on HRV and both race and sex have been conflicting. Our prior data from a convenience sample of patients undergoing clinical ambulatory ECG similarly showed lower HRV in African-Americans after controlling for co-morbidities and health behaviors (21), as have other studies (71). A recent meta-analysis concluded that African-Americans have greater HRV than Caucasians (71). The difference may lie in measures evaluated. The meta-analysis looked only short-term measures which are correlated with short-term vagal activity, including HF and time-domain measures of short-term vagal activity. Both our prior and the current study focused on longer-term measures which may reflect overall autonomic balance. These studies also did not show differences in HF. Consistent with prior research on older age effects on HRV (72), we also found older age to significantly contribute to lower HRV in the presence of stress measures and other demographic and behavioral risk variables. However, it is important to note that the current sample included a young to middle age group and it is remarkable that age effects were also highly significant in this relatively healthy and young group of community adults.

Similarly, data differ on whether and how sex influences HRV. Among studies of 24-hour HRV, many have shown lower values in women (72–74), similar to our findings, while others show lower values in men (75). One study found lower HRV in women only among those under 30 years, close to the mean age in our study (72). In a quantitative review of 44 studies including over 21,000 individuals undergoing measurement of short-term HRV (76), all time domain indices were lower in women. Among frequency domain measures, there was significant heterogeneity in findings regarding sex, which are not well-explained. For example, studies using natural-log normalized data (as ours) showed both HF and LF to be lower in women, but non-log-normalized data showed these indices lower in men. In our study, chronic stress was higher in women, as previously reported. For example, in prior studies, women demonstrate greater emotional reactivity to negative events than men, and also experience more prolonged negative emotions following negative life events (77, 78). As stress was related to HRV similarly in men and women (ie, interaction testing was negative), this may explain in part why HRV was lower in the women.

The finding that cumulative stress (as measured here by the CAI total scale) is associated with lower HRV in a healthy population, beyond effects of behavioral influences, also has clinical implications. Most preventative efforts in the general population aimed at decreasing cardiovascular morbidity and mortality focus on health behaviors such as smoking cessation and weight loss. While stress variables impacted HRV less than demographic variables, unlike demographic factors, stress is potentially modifiable. Data are accumulating that stress management techniques may also play a role in improving cardiovascular outcomes in patients with cardiovascular disease (79, 80). However, while American Heart Association recommendations (81) for those with risk factors mention stress management, AHA

recommendations for risk reduction in the general population do not (47). Our data support the importance of further studies evaluating the role of stress management as primary prevention against cardiovascular disease in healthy individuals.

Limitations

This was a cross-sectional study and thus whether stress is causative in lowering HRV cannot be determined. While it is unlikely that autonomic factors would result in the types of adverse events and stressors measured by the CAI, it is possible that other processes may influence both. This cohort was predominantly high-school educated, which may explain the absence of an effect of education on HRV, which has been seen in prior studies (21). Alcohol consumption levels were in the low to moderate range which may explain a lack of effect of alcohol use. Mean age in this study was 29 years. Whether a similar relationship between stress and HRV exists in older individuals requires further study.

The current community sample was free of physical and psychiatric disorders excluded by the SCID-IV-TR, suggesting that anxiety and depression, shown to impact HRV in other studies (56, 57), were not a primary driver of the associations seen. However, the possibility that more highly stressed individuals have pre-clinical or undiagnosed disease, including subthreshold anxiety and depressive symptoms, which would not be captured by SCID clinical diagnostic assessment, cannot be excluded. Health behaviors measures included most of the key behaviors identified by the AHA (47) (smoking, BMI, alcohol), but did not include specifics of diet, nor habitual physical exercise. Acute exercise which was not controlled can also influence HRV (82). Similar to other studies using 24-hour recordings, HF was not associated with psychosocial factors (31). This may be due to nonstationarity of HF over a 24 hour period.

Conclusion

In this study of healthy volunteers, HRV was modestly, but significantly, associated with higher levels of cumulative stress and chronic stress as measured by those respective scales. Even after accounting for the effects of demographic and behavioral risk factor variables, significant relationships between stress and the specific HRV measures of SDNN and ULF were seen. These results are consistent with the possibility that cumulative stress may contribute to poor cardiovascular outcomes through autonomic dysregulation. Whether preventive efforts to decrease coronary morbidity and mortality in the healthy population should include stress management requires further study.

Acknowledgments

This work was funded by NIH/NCRR UL1 DE019586 and PL1-DA024859 (PI Sinha). The funding source had no role in analysis of the data or preparation of the manuscript.

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Table 1

Demographic, Behavioral, and Psychological Characteristics of the Sample

Variable	Value	Women (N=70)	Men (N=87)
Age		28.94 (1.14)	29.72 (0.85)
Smoker	**No**	53 (76%)	70 (80%)
	Yes	17 (24%)	17 (20%)
Years of Education		14.91 (0.27)	15.17 (0.23)
Education	**<=12 years**	11 (16%)	12 (14%)
	> 12 years	59 (84%)	75 (86%)
Race	**African American**	16 (23%)	14 (16%)
	White	41 (59%)	65 (75%)
	Other	13 (19%)	8 (9%)
Alcohol Use Days in Past Month **		3.7 (4.3)	9.4 (7.3)
BMI		28.2 (0.69)	27.47 (0.57)
Total Cumulative Stress (Total CAI)		0.47 (0.34)	−0.38 (0.28)
Cumm Adv. Life Events (CALE)		0.26 (0.26)	−0.21 (0.23)
Chronic Stress *		0.22 (0.14)	−0.17 (0.09)

Note: Stress measures were transformed to standardized z scores for comparability across measures

Values represent mean (SD) or N (percent); BMI, body mass index.

* <.05,

** <.001

Table 2

Effects of Demographic and Behavioral Risk Factors on HRV Measures

Risk Factor	HRVs	Women (N=70)	Men (N=87)	p *
Sex	SDNN	132.34 (4.61)	160.26 (5.28)	<.0001
	ln_ULF	9.18 (0.08)	9.58 (0.07)	<.0001
	ln_VLF	7.45 (0.08)	7.95 (0.07)	<.0001
	ln_LF	6.81 (0.08)	7.28 (0.07)	<.0001
	ln_HF	6.2 (0.14)	6.49 (0.11)	0.21
Risk Factor	**HRVs**	**Non Smoker (N=122)**	**Smoker (N=34)**	**p ***
Smoker	SDNN	150.26 (4.23)	138.95 (7.89)	0.20
	ln_ULF	9.44 (0.06)	9.26 (0.11)	0.10
	ln_VLF	7.82 (0.06)	7.4 (0.12)	0.00
	ln_LF	7.16 (0.06)	6.75 (0.14)	0.01
	ln_HF	6.48 (0.09)	5.91 (0.21)	0.01
Risk Factor	**HRVs**	**Education <=12 years (N=23)**	**Education >12 years (N=134)**	**P ***
Education	SDNN	140.67 (8.28)	149.04 (4.14)	0.45
	ln_ULF	9.24 (0.12)	9.43 (0.06)	0.12
	ln_VLF	7.59 (0.12)	7.75 (0.06)	0.17
	ln_LF	6.96 (0.15)	7.09 (0.06)	0.38
	ln_HF	6.31 (0.18)	6.37 (0.09)	0.66
Risk Factor	**HRVs**	**Caucasian (N=105)**	**African American (N=30)**	**p ***
Race	SDNN	153.59 (4.78)	131.8 (6.4)	0.06
	ln_ULF	9.48 (0.07)	9.17 (0.11)	0.08
	ln_VLF	7.84 (0.07)	7.49 (0.11)	0.01
	ln_LF	7.18 (0.07)	6.82 (0.11)	0.01
	ln_HF	6.41 (0.11)	6.32 (0.18)	0.63
Risk Factor	**HRVs**	**Estimate (Beta)**	**F value (DF=1)**	**p ****
BMI	SDNN	−1.32	3.89	0.05
	ln_ULF	−0.01	1.42	0.24
	ln_VLF	−0.03	6.74	0.01
	ln_LF	−0.03	10.3	0.00
	ln_HF	−0.03	3.85	0.05
Risk Factor	**HRVs**	**Estimate (Beta)**	**F value (DF=1)**	**p ****
Days in Past Month Drinks	SDNN	0.40	0.51	0.47
	ln_ULF	0.01	2.39	0.12
	ln_VLF	0.02	4.47	0.04
	ln_LF	0.02	4.02	0.05
	ln_HF	−0.01	0.17	0.68

All values represent mean ± SE except BMI and Alcohol use Days in Past Month;

*ANOVA analysis;

**SDNN, standard deviation of NN intervals; ULF, ultra-low frequency power;

VLF, very-low frequency power; LF, low frequency power; HF, high frequency power; Regression analysis

Table 3

Relationships between Cumulative Stress and HRV Measures

Stress Measures	HRVs	Beta	F Value (DF=1)	p*	Pearson Correlation
Total Cumulative Stress (Total CAI)	SDNN	−4.04	9.28	0.00	−0.24
	ln ULF	−0.06	8.1	0.01	−0.22
	ln_VLF	−0.06	10.74	0.00	−0.26
	ln_LF	−0.06	9.2	0.00	−0.24
	ln_HF	−0.05	3.1	0.08	−0.14
Cumulative Adverse Life Events (CALE)	SDNN	−4.12	6.0	0.02	−0.20
	ln_ULF	−0.05	4.29	0.04	−0.16
	ln_VLF	−0.07	7.19	0.01	−0.21
	ln_LF	−0.06	5.23	0.02	−0.19
	ln_HF	−0.05	1.81	0.18	−0.11
Chronic Stress	SDNN	−10.68	8.64	0.00	−0.23
	ln ULF	−0.18	10.52	0.00	−0.25
	ln_VLF	−0.16	9.28	0.00	−0.24
	ln_LF	−0.18	10.7	0.00	−0.25
	ln_HF	−0.16	3.52	0.06	−0.15

*Simple Regression analysis where HRV and stress variables are analyzed as continuous variables;

Abbreviations as in Table 1 and 2

Table 4

Linear Hierarchical Regression Analyses for SDNN for each Stress and Other Demographic and Behavioral Risk Measures

Variable Entered	Beta	t Value	Beta	t Value	Beta	t Value
	TOTAL STRESS		**CHRONIC STRESS**		**CALE**	
	Block 1 (Model F=9.74***)		Block 1 (Model F=8.51***)		Block 1 (Model F=6.5**)	
	Adj R-Sq: 0.05		Adj R-Sq: 0.05		Adj R-Sq: 0.03	
Intercept	147.81	40.67***	147.81	40.52***	147.81	40.27***
Stress	−4.16	−3.12***	−10.67	−2.92***	−4.31	−2.55
	Block 2 (Model F= 15.53***)		Block 2 (Model F=15.24***)		Block 2 (Model F=13.8***)	
	Adj R-Sq: 0.16		Adj R-Sq: 0.15		Adj R-Sq: 0.14	
Intercept	200.23	16.44***	201.19	16.53***	200.92	16.35***
Stress	−3.68	−2.92***	−9.75	−2.83**	−3.73	−2.34*
Age	−1.78	−4.49***	−1.82	−4.57***	−1.81	−4.51***
	Block 3 (Model F=16.8***)		Block 3 (Model F=16.32***)		Block 3 (Model F=16.07***)	
	Adj R-Sq: 0.23		Adj R-Sq: 0.23		Adj R-Sq: 0.22	
Intercept	161.08	10.64***	162.35	10.66***	159.98	10.52***
Stress	−2.89	−2.37*	−7.13	−2.12*	−3.02	−1.98*
Age	−1.87	−4.93***	−1.90	−5.00***	−1.89	−4.96***
Sex	26.90	4.03***	26.62	3.95***	27.98	4.20***
	Block 4 (Model F=8.9***)		Block 4 (Model F=8.64***)		Block 4 (Model F=8.57***)	
	Adj R-Sq: 0.23		Adj R-Sq: 0.23		Adj R-Sq: 0.23	
Intercept	167.93	7.88***	170.91	8.01***	168.06	7.84***
Stress	−2.81	−2.22*	−6.69	−1.94*	−2.91	−1.86
Age	−1.86	−4.66***	−1.87	−4.66***	−1.86	−4.65***
Sex	26.06	3.89***	25.78	3.81***	27.00	4.03***

Variable Entered	Beta	t Value	Beta	t Value	Beta	t Value
	TOTAL STRESS		CHRONIC STRESS		CALE	
Race	−14.04	−1.67	−13.78	−1.63	−14.48	−1.71
BMI	−0.15	−0.23	−0.22	−0.36	−0.19	−0.30
Smoker	3.49	0.42	2.38	0.29	2.43	0.29

* p<0.05,

** p<0.01,

*** p<0.001

Table 5

Linear Hierarchical Regression Analyses for ULF for each Stress and Other Demographic and Behavioral Risk Measures

Variable Entered	Beta	t Value	Beta	t Value	Beta	t Value
	TOTAL STRESS		CHRONIC STRESS		CALE	
	Block 1 (Model F=8.1 **)		Block 1 (Model F=10.52 **)		Block 1 (Model F=4.29 *)	
	Adj R-Sq: 0.04		Adj R-Sq: 0.06		Adj R-Sq: 0.02	
Intercept	9.40	172.64 ***	9.40	173.94 ***	9.40	170.60
Stress	−0.06	−2.85 **	−0.18	−3.24 ***	−0.05	−2.07 *
	Block 2 (Model F=9.75 ***)		Block 2 (Model F=11.26 ***)		Block 2 (Model F=7.85 **)	
	Adj R-Sq: 0.10		Adj R-Sq: 0.12		Adj R-Sq: 0.08	
Intercept	9.99	53.32 ***	10.00	53.9 ***	10.01	52.83
Stress	−0.05	−2.66 **	−0.16	−3.15 ***	−0.05	−1.89
Age	−0.02	−3.3 ***	−0.02	−3.36 ***	−0.02	−3.34 ***
	Block 3 (Model F=11.44 ***)		Block 3 (Model F=12.12 ***)		Block 3 (Model F=10.54 ***)	
	Adj R-Sq: 0.17		Adj R-Sq: 0.18		Adj R-Sq: 0.16	
Intercept	9.44	40.05 ***	9.47	40.28 ***	9.42	39.73
Stress	−0.04	−2.13 *	−0.13	−2.51 **	−0.04	−1.52
Age	−0.02	−3.61 ***	−0.02	−3.65 ***	−0.02	−3.65 ***
Sex	0.38	3.64 ***	0.36	3.49 ***	0.40	3.81 ***
	Block 4 (Model F=6.14 ***)		Block 4 (Model F=6.44 ***)		Block 4 (Model F=5.73 ***)	
	Adj R-Sq: 0.17		Adj R-Sq: 0.17		Adj R-Sq: 0.15	
Intercept	9.39	28.24 ***	9.42	28.54 ***	9.39	28.05
Stress	−0.04	−2.01 *	−0.12	−2.35 *	−0.03	−1.41
Age	−0.02	−3.5 ***	−0.02	−3.52 ***	−0.02	−3.48 ***
Sex	0.37	3.53 ***	0.35	3.39 ***	0.38	3.68 ***
Race	−0.21	−1.59	−0.20	−1.53	−0.21	−1.63
BMI	0.00	0.44	0.00	0.39	0.00	0.34

Variable Entered	Beta	t Value	Beta	t Value	Beta	t Value
	TOTAL STRESS		CHRONIC STRESS		CALE	
Smoker	0.00	0.01	0.00	−0.02	−0.02	−0.15

* p<0.05

** p<0.01

*** p<0.001

Table 6

Linear Hierarchical Regression Analyses for VLF for each Stress and Other Demographic and Behavioral Risk Measures

Variable Entered	Beta	t Value	Beta	t Value	Beta	t Value
	TOTAL STRESS		CHRONIC STRESS		CALE	
	Block 1 (Model F=10.85***)		Block 1 (Model F=9.34***)		Block 1 (Model F=7.28**)	
	Adj R-Sq: 0.06		Adj R-Sq: 0.05		Adj R-Sq: 0.04	
Intercept	7.73	146.43***	7.73	145.76***	7.73	144.84***
Stress	−0.06	−3.29***	−0.16	−3.06***	−0.07	−2.7**
	Block 2 (Model F=11.08***)		Block 2 (Model F=10.58***)		Block 2 (Model F=9.28**)	
	Adj R-Sq 0.11		Adj R-Sq 0.11		Adj R-Sq 0.10	
Intercept	8.30	45.62***	8.31	45.66***	8.31	45.23***
Stress	−0.06	−3.11***	−0.15	−2.95***	−0.06	−2.51**
Age	−0.02	−3.26***	−0.02	−3.35***	−0.02	−3.29***
	Block 3 (Model F=16.68***)		Block 3 (Model F=15.98***)		Block 3 (Model F=15.95***)	
	Adj R-Sq: 0.23		Adj R-Sq: 0.22		Adj R-Sq: 0.22	
Intercept	7.60	34.4***	7.61	34.21***	7.58	34.17***
Stress	−0.04	−2.5**	−0.11	−2.14*	−0.05	−2.12*
Age	−0.02	−3.79***	−0.02	−3.86***	−0.02	−3.82***
Sex	0.48	4.95***	0.48	4.86***	0.50	5.12***
	Block 4 (Model F=10***)		Block 4 (Model F=9.8***)		Block 4 (Model F=9.8***)	
	Adj R-Sq: 0.26		Adj R-Sq: 0.25		Adj R-Sq: 0.25	
Intercept	7.87	25.74***	7.90	25.85***	7.87	25.64***
Stress	−0.03	−1.75	−0.07	−1.5	−0.03	−1.48
Age	−0.02	−3.04***	−0.02	−3.04***	−0.02	−3.03***
Sex	0.46	4.78***	0.46	4.71***	0.47	4.9***
Race	−0.18	−1.47	−0.18	−1.45	−0.18	−1.51
BMI	−0.01	−1.02	−0.01	−1.13	−0.01	−1.07

Variable Entered	Beta	t Value	Beta	t Value	Beta	t Value
	TOTAL STRESS		CHRONIC STRESS		CALE	
Smoker	−0.24	−2.03*	−0.26	−2.15*	−0.25	−2.13*

* p<0.05,

** p<0.01,

*** p<0.001

Table 7

Linear Hierarchical Regression Analyses for LF for each Stress and Other Demographic and Behavioral Risk Measures

Variable Entered	Beta	t Value	Beta	t Value	Beta	t Value
	TOTAL STRESS		CHRONIC STRESS		CALE	
	Block 1 (Model F=9.56***)		Block 1 (Model F=10.68***)		Block 1 (Model F=5.55*)	
	Adj R-Sq: 0.05		Adj R-Sq: 0.06		Adj R-Sq: 0.03	
Intercept	7.07	128.75***	7.07	129.19***	7.07	127.18***
Stress	−0.06	−3.09***	−0.18	−3.27***	−0.06	−2.36*
	Block 2 (Model F=17.18***)		Block 2 (Model F=18.34***)		Block 2 (Model F=14.99***)	
	Adj R-Sq: 0.17		Adj R-Sq: 0.18		Adj R-Sq: 0.15	
Intercept	7.92	43.44***	7.93	43.83***	7.93	43.01***
Stress	−0.05	−2.88***	−0.16	−3.21***	−0.05	−2.13*
Age	−0.03	−4.84***	−0.03	−4.94***	−0.03	−4.86***
	Block 3 (Model F=20.6***)		Block 3 (Model F=20.95***)		Block 3 (Model F=19.6***)	
	Adj R-Sq: 0.27		Adj R-Sq: 0.28		Adj R-Sq: 0.26	
Intercept	7.24	32.53***	7.26	32.63***	7.22	32.26***
Stress	−0.04	−2.27*	−0.12	−2.44*	−0.04	−1.72
Age	−0.03	−5.44***	−0.03	−5.51***	−0.03	−5.47***
Sex	0.47	4.75***	0.45	4.62***	0.48	4.93***
	Block 4 (Model F=12.02***)		Block 4 (Model F=12.25***)		Block 4 (Model F=11.73***)	
	Adj R-Sq: 0.30		Adj R-Sq: 0.30		Adj R-Sq: 0.29	
Intercept	7.61	24.72***	7.64	24.95***	7.62	24.62***
Stress	−0.03	−1.54	−0.09	−1.82	−0.02	−1.08
Age	−0.03	−4.58***	−0.03	−4.6***	−0.03	−4.57***
Sex	0.44	4.57***	0.43	4.44***	0.45	4.69***

Variable Entered	TOTAL STRESS		CHRONIC STRESS		CALE	
	Beta	t Value	Beta	t Value	Beta	t Value
Race	−0.18	−1.51	−0.18	−1.46	−0.19	−1.54
BMI	−0.01	−1.49	−0.01	−1.54	−0.01	−1.56
Smoker	−0.20	−1.67	−0.20	−1.7	−0.22	−1.8

* p<0.05,

** p<0.01,

*** p<0.001