Psychological and social support associations with mortality and cardiovascular disease in middle-aged American Indians: the Strong Heart Study

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Abstract

Purpose—Our study examined psychosocial risk and protective features affecting cardiovascular and mortality disparities in American Indians, including stress, anger, cynicism, trauma, depression, quality of life, and social support.

Methods—The Strong Heart Family Study cohort recruited American Indian adults from 12 communities over 3 regions in 2001–2003 ($N = 2786$). Psychosocial measures included Cohen Perceived Stress, Spielberger Anger Expression, Cook-Medley cynicism subscale, symptoms of post-traumatic stress disorder, Centers for Epidemiologic Studies Depression scale, Short Form 12-a quality of life scale, and the Social Support and Social Undermining scale. Cardiovascular events and all-cause mortality were evaluated by surveillance and physician adjudication through 2017.

Results—Participants were middle-aged, 40% male, with mean 12 years formal education. Depression symptoms were correlated with anger, cynicism, poor quality of life, isolation, criticism; better social support was correlated with lower cynicism, anger, and trauma. Adjusted time-to-event regressions found that depression, (poor) quality of life, and social isolation scores formed higher risk for mortality and cardiovascular events, and social support was associated with lower risk. Social support partially explained risk associations in causal mediation analyses.

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Declarations

Conflict of interest The authors have no conflicts to report.

Conclusion—Altogether, our findings suggest that social support is associated with better mood and quality of life; and lower cynicism, stress, and disease risk—even when said risk may be increased by comorbidities. Future research should examine whether enhancing social support can prospectively reduce risk, as an efficient, cost-effective intervention opportunity that may be enacted at the community level.

Keywords

Social support; Stress; Depression; Quality of life; Cardiovascular disease; Mortality

Introduction

Disparities in cardiovascular disease (CVD) outcomes persist by sex, race, and ethnic groups [1, 2]. American Indians have a disproportionately high burden of CVD, with risk reports chiefly focused on conventional clinical determinants including hypertension, diabetes, and obesity [3]. Psychosocial exposures such as historical traumas, chronic stress, and other psychological or social determinants have been linked to increased risk of adverse CVD outcomes in other groups [4, 5], but remain unexplored in American Indians.

Most people will be exposed during their lifetime to at least one potentially life-threatening or traumatic experience; other stressors can be ongoing, such as exposure to bullying, harassment, dysfunctional relationships, or poverty. When stress is especially intense, chronic, uncontrolled, or overwhelming, deleterious effects on health or psychology may include atherosclerosis [6, 7] and CVD [8, 9], cognitive impairment and dementia [10–12], physical disability [13–16], depression [17–19], and low quality of life [20, 21]. Postulated biological mechanisms or mediators for these observed associations include inflammation, autonomic nervous system dysregulation, and endothelial dysfunction, although some of the mechanistic relationships are likely to be circular and multi-causal, including depression, inflammation, and cardiovascular risk. [22, 23].

In addition, adaptive or maladaptive behaviors resulting from trauma or stress exposures, which may also mediate disease associations, include poor health habits, bad sleep hygiene, reluctance to change unhealthy lifestyle behaviors, non-adherence to medical treatment, high-risk lifestyle behaviors, and poor social bonding [24]. In particular, social and socioeconomic isolation either persists or has increased over the last several decades, particularly for individuals with limited resources, despite programs and policies aimed at social integration and mobility [25]. A recent report comparing U.S. healthcare metrics by race and by state [26] suggests that disparities affecting American Indian, Alaska Native, and African American people are particularly stark, with average mortality 5 years shorter than non-Hispanic Whites, driven in part by social factors such as proximity to care. However, in some rural counties, life expectancy is especially low: 37–45 years among some American Indian males in the Northern Plains and 39–43 among some African American males in the South and Mid-Atlantic [27]. Despite such substantial structural social inequities, a recent review found no studies addressing social isolation in rural settings, suggesting important oversights in addressing the underlying causes and contributions to social and health inequity [28]. Furthermore, to our knowledge, no large, population-based

study has addressed the associations among stress, resilience, social support, and related features among American Indian adults.

Underrepresentation of American Indian peoples in social and health research is problematic because distinctive healthcare systems [29–32], sociodemographics [33, 34], environmental [35–37], clinical [38–47], cognitive [48, 50], and neurological risk profiles [51–56] are likely to result in unique patterns of association as well as health trajectories. Furthermore, historical traumas can be felt through multiple generations, with tangible effects on individual biology as well as intergenerational familial, community, and social structures. The well-known and well-documented US federal policies affecting American Indian peoples as communities, including forced relocations, tribal treaty violations, and discriminatory institutional practices continue in some cases through the present day. For example, the Indian Boarding Schools program, run by the Bureau of Indian Affairs within the US Department of the Interior, compelled attendance, often at great distance from home, with little or no contact with their families, focused on societal assimilation with little attention to quality of education [57], prohibiting cultural and linguistic expression [58], and employing harsh, militaristic disciplinary techniques, resulting in high prevalence of traumatic stress disorders, depression, [59] illness, and death [60]. The social and psychological impact of these experiences on surviving children, families, communities, and culture have been profound [61]. Parental right to refuse attendance was only granted in 1978, when attendance was near its peak at around 60–70,000 children per year. [62].

Despite such patterns of risk—and although communities and tribes may differ—American Indian peoples and populations have largely displayed remarkable resilience to stress and trauma [63, 64]. In studies among Diné people, such resilience has been attributed to *Hózhó*, a strength-based wellness philosophy emphasizing the wholeness of person and community and valuing engagement in cultural, social, and familial structures [63, 65–68]. In studies of youth, up to 30% of the variance in physical and emotional health may be attributed to this type of psychological resilience and related cultural perspectives, with a substantial portion relying on family caring and social support [21, 69, 70]. However, risk or protection features related to stress, resilience, and social support among older American Indians have not been quantified.

This study explores features that promote resilience, including social support, and features that may inhibit resilience or result from excess trauma, such as perceived stress, anger, cynicism, depression, and poor perceived quality of life; and to establish these features in association with CVD and mortality outcomes among older American Indians. Our ultimate hypothesis is that potential negative psychological influences on health may be modified or even interrupted by positive psychological influences, suggesting that health risks may be ameliorated somewhat through targeted, culturally appropriate interventions. This work has the potential to advance public health knowledge on innovative risk and protective features in a vulnerable population.

Methods

Study setting

The Strong Heart Study (SHS) encompasses the largest population-based cohort of American Indians ever recruited, with 4549 enrolled beginning in 1989–1991 from 13 tribal communities across the Northern Plains, Southern Plains, and Southwest regions representing 67% of eligible residents then aged 35–75 years. [71] Study examinations included several waves of longitudinal data collection over the subsequent 3 decades, focused chiefly on CVD and diabetes risk, with 85–87% successful recruitment and participation at each subsequent examination visit [71]. Continuous morbidity and mortality surveillance with physician committee based adjudication for CVD and stroke events have been conducted, with complete assessment currently available through December 31, 2017 [40, 56]. The Strong Heart Family Study (SHFS) was an expansion cohort that recruited an additional 3838 related family members at SHS Exam 4 (2001–2003). One of the participating communities has subsequently withdrawn from all research, and their data have been excluded from analyses, resulting in a maximum SHS/SHFS overlapping $N = 2786$. Detailed recruitment methods for SHS and SHFS, including informed consent and ethical review procedures, have been previously published [71, 72].

Timeline and inclusion

Our analyses used the psychosocial data collected at the SHS Exam 2 (1993–1995) and at the SHFS Exam 4 (2001–2003), and the continuous morbidity and mortality surveillance data (through 2017). Inclusion criteria for our analyses are: participation in the SHS Exam 2 visit + SHFS Exam 4 visit, and no prior CVD or stroke event. All participants spoke fluent English; all examinations were conducted in English.

Psychosocial scales

Few standard measures have been psychometrically or theoretically validated among American Indians. Our research team has recently conducted preliminary psychometric assessments of two instruments, as noted below. However, most such measures have unknown performance characteristics. The stress scale was measured at the SHS Exam 2; all others were measured at SHFS Exam 4.

Perceived stress—On the original 10-point Cohen Perceived Stress Scale (PSS) [73], each item is rated on a 5-point scale (0–4), with ratings summed to create a total ranging from 0 to 40. Scores of 13 are considered average; scores of 20 or higher are considered high stress [74]. Our data included 7 of the original 10 questions; we adjusted our total scores by a factor of 10/7 to allow for comparability with previous studies.

Anger management and expression—The Spielberger Anger Expression (S-AX) [75, 76] scale is comprised of 20 questions on a 4-point scale (1–4). Three subscales (AX-In: likelihood of concealing anger, 9-item; AX-Out: likelihood of being hostile, 8-item; AX-Control, 3-item: extent of ability to control own anger) [77] and total summary score represent facets of anger management and experience. We focused our analyses on the

AX-Out, AX-In, and AX-Control sub-scores separately due to psychometric differences in withholding, expressing, or controlling anger.

Cynicism—Originally developed for the Minnesota Multiphasic Personality Inventory, the Cook-Medley hostility scale (Cook) [78, 79] consisted of 50 items, divided across 6 subscales (cynicism, hostile attributions, hostile affect, aggressive responding, social avoidance, and other) [77]. Our data collections included only the 8-item cynicism subscale (Cook-C); each item was scored on a binary scale (0,1) and summed across items for a total score ranging from 0 to 8.

Trauma—Similar to other scales used to assess post-traumatic stress disorder (PTSD), our unvalidated set of questions assessed symptoms of trauma and stress, focused on recurrent thoughts, disruption of sleep, and sustained anxiety related to one or more past events and lasting for at least one month. Nine (9) items were coded on a binary scale (0,1) and summed for a total score ranging from 0 to 9.

Depression—The Center for Epidemiologic Studies Depression (CES-D) scale is a screening tool for depression and depressive symptoms [80], and among the most widely used instruments in clinical medicine and psychiatry [81, 82]. The original scale consists of 20 items assessing symptoms of depression, with responses scored on a 4-point scale (0 to 3), and 4 items reverse-coded. Possible summary total scores range from 0 to 60, with scores 16 considered to be evidence of depressive symptoms [83]. Our team previously reported CES-D scores among American Indians aged 65–95 years mean 11 (SD 8) for the 20-item scale. [84].

Quality of life—The Short Form 12-question (SF-12) survey [85], a measure of health-related quality of life, is a 12-item scale with varying item coding among multiple subscales, including general health perceptions, vitality, bodily pain, physical function, emotional function, social function, and mental health. Items are coded (or reverse coded) so that higher scores corresponding to worse health, and each item is scored with a minimum score of 1, so that the total possible summary scores range from 12 to 47. In comparison to the longer SF-36 [86], SF-12 had similar score performance but larger standard errors.

Social support—Social support and social undermining (SS/U) [87, 88] were measured using 20 items derived from the National Comorbidity Survey, tailored specifically for American Indian populations, and then validated by the American Indian Service Utilization and Psychiatric Epidemiology Risk and Protective Factors Project [89]. Positive subscales covered emotional support (6 items coded 1–3) and instrumental support (5 items coded 0,1), with higher scores connoting better social support; negative subscales covered critical appraisal (6 items coded 1–3) and isolation (3 items coded 1–3), with higher scores connoting poorer social support or greater isolation. Summary scores accounting for reverse coding included the four subscales together, with a possible range 15–50.

Outcome Measures: Event surveillance and physician adjudications for clinical events were conducted by the SHS morbidity and mortality events committee and include events from before the SHS baseline visit (1989–1991) through December 31, 2017 [40], although

events occurring before the time of the visit when the relevant exposure variable was measured were excluded. Surveillance methods used to identify possible events included telephone contact, interim clinic visits, and mailed questionnaires for self-report. Paper and electronic medical records at the Indian Health Service (IHS) and local non-IHS hospitals and patient care facilities were also reviewed for possible events including ICD-9 codes as well as and manual review of participant records by field staff for specific terminology (e.g. subarachnoid, intracerebral, or intracranial occlusion of cerebral or precerebral arteries including embolism or thrombosis, cerebral ischemia, stroke, cerebral atherosclerosis, hypertensive encephalopathy, and unspecified lesions). The adjudication process started with abstraction of complete records including medical history, physical examination, emergency room visit, medical consult, medical imaging, discharge summary, operation and other procedure reports, for all surveillance-identified possible events. A committee of physicians then reviewed and discussed all possible events, with consensus decision as possible, probable, or definite event.

Other measures

All participant characteristics were measured at the SHFS Exam 4 (2001–2003), when the majority of the psychosocial scales were collected. Field center was defined by geographic region. Participants self-reported age (years), sex (male, female), annual household income, years of formal education, and daily medication use. Waist and hip circumference, height, and weight were measured using standard anthropometric techniques, with body mass index (BMI) defined as weight in kilograms divided by height in meters, squared. Blood pressure was measured by sphygmomanometry, with the average of the second and third seated measure recorded. Blood samples were collected to measure fasting plasma glucose, serum cystatin C and creatinine, C-reactive protein (CRP), interleukin-6 (IL-6), and plasminogen activator inhibitor 1 (PAI-1). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI 2012 equation (using both serum creatinine and cystatin C). Diabetes mellitus was defined as fasting plasma glucose 126 mg/dL or use of insulin or oral diabetes medications. Hypertension was defined as measured systolic blood pressure 140, diastolic blood pressure 90, or use of antihypertensive medications.

Statistical analyses

Descriptive statistics (mean, standard deviation, count, percent) were used to summarize selected participant characteristics—including sociodemographics, anthropometrics, clinical covariates, lab assays, and psychosocial scales—at the time of the SHFS Exam 4 visit (2001–2003) among all available participants ($N = 2,786$). Histograms for psychosocial scale scores were used to graphically examine the range and distribution of these measures, in this understudied population. Standardized (Z scored) Pearson product-moment correlation coefficients (rho) were used to evaluate unadjusted associations between combinations of psychosocial scale measures, with graphical display based on color range for different values of rho. Cox proportional hazards time-to-event regressions evaluated risk of all-cause mortality or composite CVD event (myocardial infarction, congestive heart failure, stroke) [90] outcomes for each standardized psychosocial scale individually, with hazard ratios (and 95% confidence intervals) calculated per standard deviation on the Z-scale, to allow for direct comparability across all exposure measures. Participants with death

or CVD outcomes that occurred before the end of the relevant exposure examination were excluded; exclusions were done separately for each model. Adjustment covariates were age, sex, education, income, and site (Model A); lab measures related to inflammation, diabetes, and hypertension–which may develop as a result of chronic stress, and may, therefore, lie in the causal pathway—were additionally included in Model B. Causal mediation analysis [91], a method that parses a single estimate of association into both direct and indirect estimates, with the indirect effect attributed to the mediator, was conducted for the exposures that had consistent patterns of significant findings with mortality in the Cox models, with calculation of the coefficient for the exposures with and without the mediator in the model as well as calculation of the estimated percent of effect mediated, using quasi-Bayesian Monte Carlo algorithm with 1000 replications/simulations. Missingness varied among different features, but was overall low and noninformative. Because exposures are strongly correlated, P value adjustment such as Bonferroni ($P < 0.003$) would be overly conservative. To protect against the problem of multiple comparisons in this non-independent testing context, we evaluated findings using a Bayesian framework, based on consistency and clinical interpretability of the full range of findings (family-wise error), rather than by adjustment of individual single P values, to ensure appropriate inference and reduced likelihood of Type I error.

Results

SHFS Exam 4 participants were generally middle-aged, mean age 40.8 years; approximately 40% were male (Table 1). On average, participants had equivalent of a high school education and below-average annual household income, although there was large variance. The waist–hip ratio and body mass index was generally high, with majority considered obese. Systolic blood pressure and glomerular filtration rate were generally not abnormal, but nearly 20% of participants had diabetes and 32% hypertension. CRP was generally high, with wide variability (reference range < 3 mg/L); IL-6 was generally normal (reference range < 16.4 pg/mL), but some participants had very high values—more than 2,000; PAI-1 was overall high (reference range 2–15 AU/mL).

Psychosocial scale means, ranges, and distributions are shown in Table 1 and Fig. 1. Cohen perceived stress scale (PSS) was generally normally distributed, with observed range truncated to being somewhat lower than maximal possible range. Spielberger Anger Expression (AX) subscale scores were left-skewed with most scores corresponding to less extreme scores on anger expression. Cook-Medley Hostility scale cynicism subscale (Cook-C) scores were somewhat bimodal, with many scoring 0, but otherwise distributed normally. Post-traumatic stress disorder (PTSD, trauma) symptoms scores were somewhat uniformly distributed across the entire range of possible symptoms. CES-D depression scale scores and SF-12 quality of life scores were left-skewed, with most scores corresponding to fewer symptoms or better quality of life, respectively. Finally, social support subscales were skewed with the largest number of scores corresponding to stronger social support.

Especially strong (rho > 0.6) positive correlations between scales (Fig. 2) include stress-trauma, anger out-anger in, anger in-depression, anger in-instrumental social support, anger in-social isolation, cynicism-depression, trauma-social isolation, depression-poor quality of life, depression-social criticism, depression-social isolation, poor quality of life-social

criticism, emotional-instrumental support, emotional-total social support, instrumental-total social support. Especially strong (rho < − 0.6) negative or inverse correlations include cynicism-total social support, depression-emotional support, depression-total social support, poor quality of life-emotional support, poor quality of life-total social support, social criticism-total social support.

For time-to-event analyses, we followed $N = 2786$ participants with 480 failures for mortality over 40,106.1 person-years (12 deaths per 1000 person-years) and with 299 failures for CVD composite events over 42,522.4 person-years (7 CVD events per 1000 person-years). Cox regressions (Table 2) showed that higher CES-D score (more symptoms of depression) and higher SF-12 score (poorer quality of life) were associated with higher risk of all-cause mortality, both without (HR 1.2, 95% CI 1.1–1.4; HR 1.5, 95% CI 1.3–1.6, respectively) and with (HR 1.3, 95% CI 1.1–1.4; HR 1.4, 95% CI 1.3–1.6, respectively) adjustment for potentially mediating clinical features as described in Methods. Higher social criticism and social isolation were also significantly associated with higher risk of mortality (HR 1.1, 95% CI 1.0–1.2; HR 1.2, 95% CI 1.1–1.3, respectively) adjusted for all features. However, more emotional support, instrumental support, and total social support were inversely associated with mortality (HR 0.9, 95% CI 0.8–1.0; HR 0.9, 95% CI 0.8–1.0; HR 0.8, 95% CI 0.8–0.9, respectively). The degree of these associations, all standardized, suggest that the strongest degree of association is for SF-12, but the associations for CES-D and Social support features are of similar magnitude. Associations for composite CVD outcome followed similar patterns, although CES-D, SF-12, and instrumental support scales were not significantly associated after adjustment for confounding and/or mediating features.

Causal mediation analyses of social support subscales (Table 3) suggest that both positive (emotional, instrumental) and negative (criticism, isolation) features partially arbitrate the associations of CES-D and SF-12 with the mortality outcome. The estimated percent of total effect mediated (arbitrated) by social support ranged from 1 to 15% for CES-D and from 0 to 4% for SF-12.

Discussion

Overall, these findings suggest that, although symptoms of stress, expressed anger, cynicism, trauma, depression, poor quality of life, social criticism, and isolation were common; emotional control and social support were also common among middle-aged American Indians. Future research may examine population features associated with each scale and psychological domain, such as features that may predict or determine better emotional or instrumental support, or more extreme social isolation. Such findings may be useful in identifying subgroups at particularly high risk, or which have particularly keen characteristics related to higher resilience.

We also found that negative psychological features correlated strongly with each other, with depression especially commonly correlated with other features; and that social support negatively correlated with most of the negative psychological features, especially depression and (poor) quality of life. Social support also correlated inversely with cynicism; anger

and trauma correlated positively with social isolation. All together these findings suggest that social support and social connectedness may be important to preventing, lowering, or improving depression, quality of life, and trauma, but that cynicism and anger may be psychological features that disrupt such social functioning. Future research identify specific subgroups at higher risk, sociological mechanisms, and potential targeted interventions.

In adjusted regressions, worse depression, poorer quality of life, social isolation, and social criticism were significantly associated with risk of mortality and CVD events, both with and without adjustment for clinical features that may mediate an inflammatory response. Furthermore, emotional and instrumental social support was associated with lower risk of these outcomes, and also partially mediated the effect for depression and quality of life scales. These findings suggest that improving social support may provide an effective opportunity to improve depression and health-related quality of life in middle-aged American Indians, with possible reduction of mortality and cardiovascular outcomes. Future research may be justified to examine the efficacy of social support programs on these and other outcomes.

The relationship between social support and CVD morbidity and mortality (particularly for coronary heart disease) has been well documented in previous studies in the general US population [92–94]. In a cohort of 1,381 African–American adults, social support was associated with preventing or delaying CVD onset [95]. Another study showed that perceived social support was associated with lower mortality among women free of CVD at baseline [96]. However, the results from those studies may not be generalizable to American Indians. To the best of our knowledge, there are no studies directly assessing the relationship between social support, CVD events, and all-cause mortality in American Indians. Additionally, comparability in effect estimates across populations is not possible due to differences in measurement scales; future research should directly compare populations for such differences.

Furthermore, the evaluation of inter-feature correlations and mediation by inflammatory features and by social support features as potential determinants of resilience have been underexplored. Antidepressants may lower inflammation and anti-inflammatory agents may reduce symptoms of depression [97], with consequent effects on vascular risk, suggesting that depression and inflammation may be key factors in the causal chain between stress, vascular or neurodegenerative brain aging, and mortality. A nationally representative longitudinal survey of adults in the United States conducted by the Survey Research Center of the University of Michigan showed that social support as a resilience factor mediated the effect of depression on coronary heart disease [98]. In comparison, our study showed a mediating effect of social support on depression and poor quality of life on mortality outcome. However, social support was an independent negative correlate for anger, trauma, and isolation as well.

Possible explanations for our findings could be the strong cultural values of community connectedness [99, 100] observed in many American Indian communities and tribes. Although culturally heterogeneous, many members strongly value family, community, and heritage—with an emphasis on multiple generations. Previous studies have shown social

support to be a protective risk factor for life satisfaction in older American Indians [70, 101, 102]. Social support, both emotional and instrumental, may reduce stress, promote cardiovascular resilience, and improve survival. Future strategies by public health and health care professionals may consider factors that promote social connectedness and reduce isolation.

As in previous studies on depression and CVD [92, 93, 103], our study showed an increased risk of CVD events and mortality in participants with greater symptoms of depression and lower quality of life. Major depressive disorder is a well-documented risk factor for incident CVD in both healthy patients and those with established CVD [92, 93, 103, 104]. Postulated mechanisms involve an interplay between a behavioral and neuroendocrine system such as medication non-adherence, sedentary lifestyle due to depressive symptoms, hyperactivity of the hypothalamic-pituitary axis, platelet activation, endothelial dysfunction, alterations in cardiac autonomic tone, increase in catecholamine and serotonin level [105]. This is the first study conducted in American Indians to show the interrelation between depressive symptoms, quality of life, social support, and CVD outcomes in healthy participants after adjusting for traditional cardiovascular risk factors. Depression and quality of life are directly related to each other, and studies have shown that treating depression could improve health-related quality of life. Future studies may focus on assessing the efficacy of cognitive-behavioral therapy and pharmacotherapy in combination with social programs on treating clinical depression, CVD, and mortality outcomes in this heavily burdened population.

In a theoretical or conceptual model of resilience or coping reserve, life stresses, conflict, trauma, and health disparities may accumulate, to cause an affected person to "run low" in resilience or coping reserve, with possible symptoms including feelings of stress, depression, anger, cynicism, and poor perceived quality of life. With the influence of positive inputs, such as social support and connectedness, such adverse effects may be counterbalanced, resulting in maintaining wellness and optimism. This framework may be used to understand the findings in this study, but may not fully explain the results. For example, we discovered that adjustment for potential mediators, including CVD comorbidities and inflammatory markers, did not change risk estimates. It is possible the salient mediators were not measured in this study, or there may be other, different health characteristics that mediate risk between social support, low quality of life, or depression, and mortality or CVD events.

Some of the findings in this study also warrant further consideration. For example, the Cook-Medley cynicism subscale was inversely correlated with many of the negative psychosocial measures. Also, the Anger-In scale was correlated with the Instrumental Social Support scale. Cynicism may vary independently, with unknown or latent determinants; and those needing or receiving tangible social support may be more likely to keep anger symptoms inside rather than expressed, to preserve their relationships. However, such suppositions are hypothetical and unexplored. Furthermore, resilience and other beneficial features, including cultural identity and participation have been unexplored. Future research efforts may benefit from more comprehensive, complete, or direct measures of such constructs.

Strengths and limitations

The strengths of this work include the comprehensive clinical and interview data collection protocols with the longitudinal evaluation of outcomes in a heterogeneous population-based recruitment setting across multiple regions, tribes, and communities. This is also the first attempt to assess psychosocial risk factors and CVD outcomes in a large longitudinal cohort of American Indians. Lastly, this is the first study in American Indians to describe social support as an independent mediator for inflammatory and stress-related exposures with significant risk for CVD and mortality outcomes.

There are also some limitations. First, although the construct of resilience was of interest, we did not directly measure individual resilience and so were limited to evaluating individual characteristics more distally related to resilience. Future research may benefit from direct measurement of resilience and other features in this and other similar populations. Also, the psychosocial exposures are measured only once; thus, these measures may not fully or accurately represent lifetime or usual exposure—which may contribute to measurement error. Further, many of these scales have not been validated in American Indians, so it is unknown to what degree they accurately represent the underlying factors that they have been developed to measure–possibly introducing errors of inference. Because American Indians comprise unique cultural, historical, educational, linguistic, psychological, and cognitive profiles, formal validations are critical to construct validity; furthermore, American Indian peoples are not homogeneous and so such validity may differ even among tribe, language group, or region. Initial assessments of the CES-D scale in this population suggest that 12 of the 20 items demonstrate reasonable measurement invariance, with further validation needed [106]. Third, without a direct measure of resilience, we implicitly assumed that the positive mediating factors evaluated are related to psychosocial resilience, based on previous reports in similar populations (in American Indians, these are mostly children). Fourth, features were measured by standardized self-report scale on questionnaire based instrument, which are common and practical tools for epidemiologic and clinic settings, but unable to replace the gold standard of full-day neuropsychological interview or direct functional testing. Finally, there may be unmeasured cultural or other resilience-related factors that independently contribute to these health outcomes, which, if true, could limit discoverability.

Future directions

Analyses examining scale validity, including measures of internal consistency and reliability, independent dimensionality, and appropriate measured and latent constructs that best capture stress and resilience-related factors, should follow. Such work requires multiple measures of a scale over time, and so follow-up measurement of these scales in this population are warranted. Future research may also benefit from direct measurement of resilience as an independent psychological construct, as well as intermediate biomarkers of stress or a larger inflammation panel that represents a larger set of systemic biological functions. Additionally, regional, cultural, or linguistic adaptation of some measurement items may be warranted. Finally, the effects of psychosocial factors on cognitive outcomes, including vascular and Alzheimer's dementia, should be evaluated due to the strong overlap with cardiovascular, metabolic, and inflammatory pathological mediators.

In summary, our findings—that social support, depression, and quality of life may be key to risk and amelioration of mortality and CVD events in this heavily burdened population—have the potential to advance public health knowledge and programs on modifiable conditions strongly related to health disparities. If improving social support and connectedness can effectively reduce mortality and CVD risk caused by stress, trauma, then intervention programs aimed at these mediating factors may represent efficient, cost-effective risk reduction opportunities that may be enacted at the community level. Our findings should encourage researchers, public health practitioners, and communities to consider social support and companionship promoting programs, among other resilience-promoting interventions, as possible tools to investigate for addressing premature mortality, cardiovascular disease, and related conditions.

Acknowledgements

Data availability

The data used in these analyses are part of a data repository for the Strong Heart Study cohort. These data are the intellectual property of the tribes from which the data were collected, and their use for analysis is contingent on formal approval procedures. For more information, please visit strongheartstudy.org.

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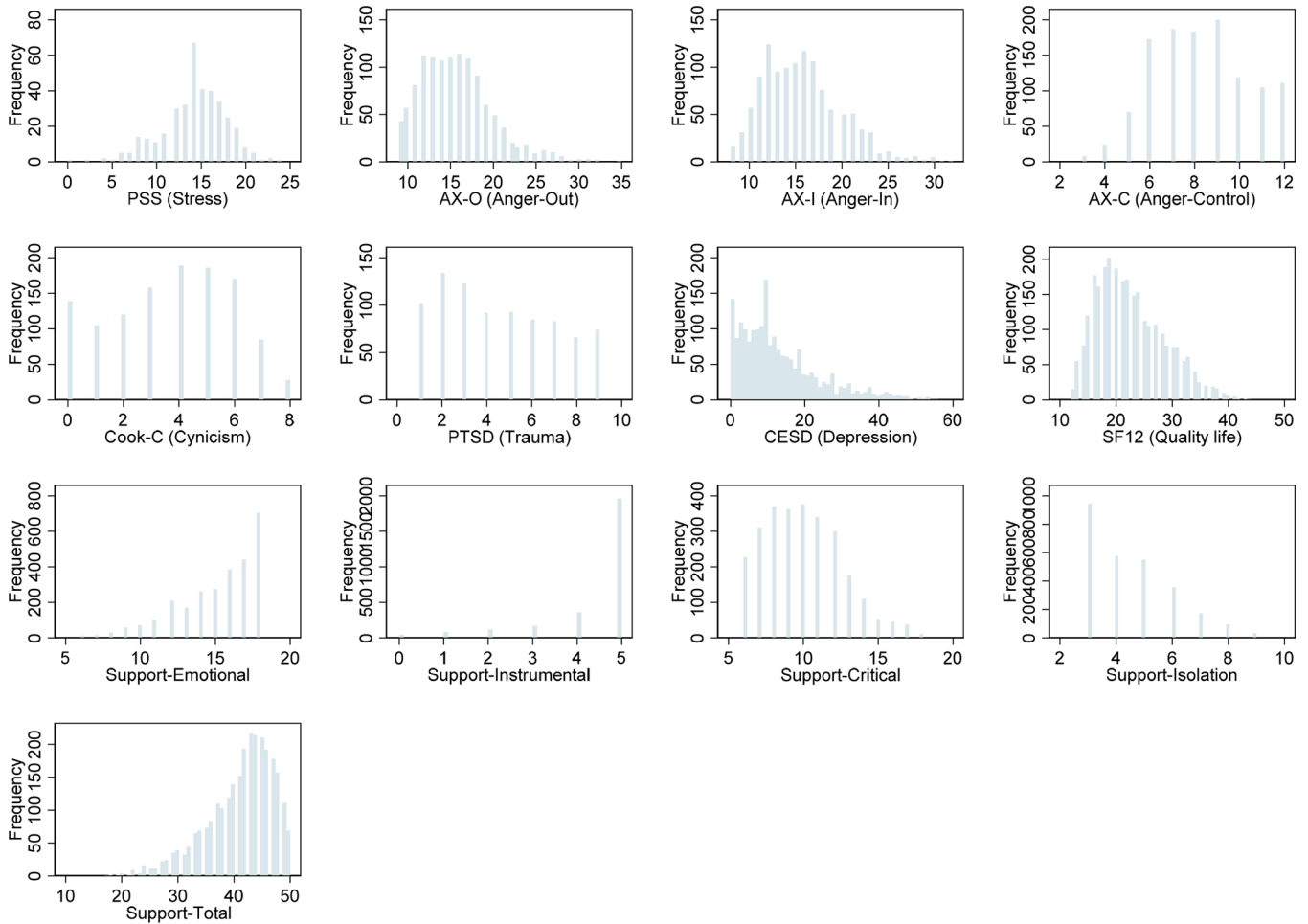
Fig. 1.

Distributions of neuropsychological and psychosocial measures among American Indian adults from the Strong Heart Family Study (2001–2003).

Legend: Histograms showing distributions of psychosocial measures, based on frequency. Measures include Cohen Perceived Stress Scale (PSS), Spielberger anger expression (AX) subscales, Cook-Medley cynicism scale, PTSD scale, Centers for Epidemiologic Studies Depression (CES-D) scale, Short Form 12 (SF) a quality of life scale, and Social Support and Social Undermining (SS/U) scale. Higher PSS scores connote higher perceived degree of life stress; higher AX-Out scores more likelihood to express anger outward; higher AX-In scores more likelihood to hide anger; higher AX-Control scores greater ability to control anger; higher Cook-C scores greater degree of cynical views or perspectives; higher PTSD score more symptoms related to traumatic experience; higher CES-D scores more symptoms of depression; higher SF-12 scores worse quality of life; higher emotional, instrumental, and total support scores greater degree of social support; higher criticism and isolation scores lower degree of social support.
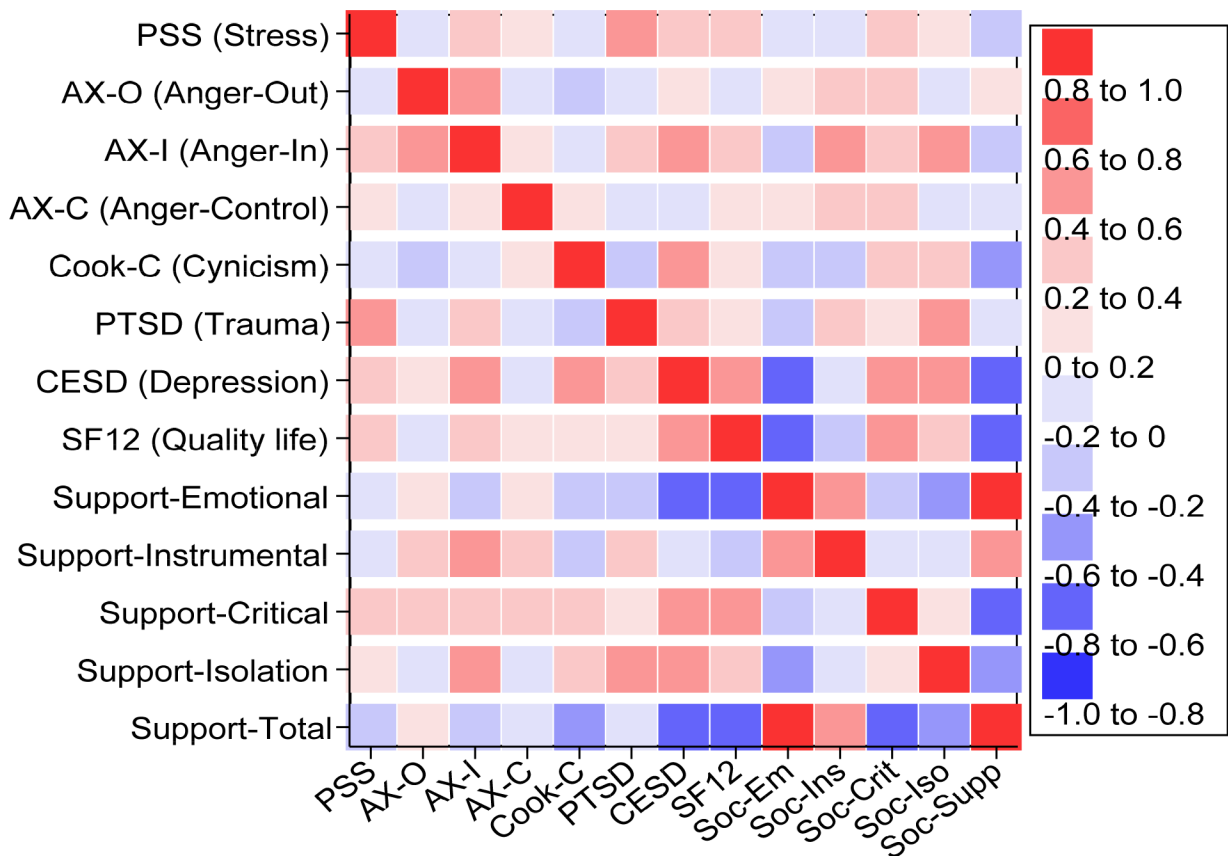
Fig. 2.
Standardized Pearson product-moment correlation coefficient heatmap among neuropsychological and psychosocial measures among American Indian adults from the Strong Heart Family Study (2001–2003).

Legend: Heatmap of Pearson correlation coefficients among standardized neuropsychological and psychosocial measures. Red indicates high degree of positive correlation and blue indicates high degree of negative correlation (inverse); with strength of coloration corresponding to coefficient indicated in legend (right). Variables all standardized (z-scored) to allow cross-comparisons. Measures include Cohen Perceived Stress Scale (PSS), Spielberger anger expression (AX) subscales, Cook-Medley cynicism scale, PTSD scale, Centers for Epidemiologic Studies Depression (CES-D) scale, Short Form 12 (SF) a quality of life scale, and Social Support and Social Undermining (SS/U) scale.

Table 1:

Selected participant characteristics of American Indians from the Strong Heart Family Study (2001–2003)

	N=2786
Age, years	40.8 (17.3)
Male, n (%)	1125 (40.4%)
Education, years	12.2 (2.3)
Annual Household Income <$20,000, n(%)	1178 (53.9%)
Southern Plains center, n (%)	1220 (43.8%)
Northern Plains center, n (%)	1210 (43.4%)
Southwest center, n (%)	356 (12.8%)
Waist-hip ratio (WHR)	0.9 (0.1)
Body mass index (BMI)	31.3 (7.5)
Systolic blood pressure (SBP), mmHg	123.0 (16.9)
Estimated Glomerular Filtration Rate (eGFR), mL/min	96.5 (26.2)
Diabetes Mellitus (DM), n (%)	529 (19.1%)
Hypertension, n (%)	886 (32.0%)
C-reactive protein (CRP), mg/L	6.6 (9.5)
Interleukin-6 (IL-6), pg/mL	12.7 (68.8)
Plasminogen activator inhibitor 1 (PAI1), AU/mL	57.2 (44.5)
Stress: PSS Score (possible range 0–40)	14.2 (3.6); 0–24
Anger: AX-Out Score (possible range 9–36)	15.7 (4.2); 9–35
Anger: AX-In Score (possible range 8–32)	15.6 (4.2); 8–32
Anger: AX-Control Score (possible range 3–12)	8.3 (2.1); 3–12
Cynicism: Cook-C (possible range 0–8)	3.7 (2.2); 0–8
Trauma: PTSD Score (possible range 0–9)	4.5 (2.5); 1–9
Depression: CESD Score (possible range 0–60)	13.1 (10.8); 0–56
Quality of life: SF-12 Score (possible range 12–47)	22.6 (6.1); 12–44
Social support-Emotional subscore (possible range 6–18)	15.2 (2.7); 6–18
Social support-Instrumental subscore (possible range 0–5)	4.4 (1.1); 0–5
Social support-Criticism subscore (possible range 6–18)	9.9 (2.6); 6–18
Social support-Isolation subscore (possible range 3–19)	4.5 (1.5); 3–9
Social support-Total score (possible range 15–50)	41.2 (6.0); 17–50

All numbers given as mean and standard deviation, unless otherwise specified. Observed range added for neuropsychological or sociocultural scales.

Table 2:

Standardized Cox proportional hazards models for time to event among American Indians in the Strong Heart Family Study (2001–2003)

All-cause mortality	Model A			Model B		
	HR	95% CI	*P-value*	HR	95% CI	*P-value*
PSS	1.06	(0.89, 1.26)	*0.498*	1.03	(0.86, 1.23)	*0.783*
AX-Out	0.98	(0.83, 1.16)	*0.812*	0.97	(0.80, 1.17)	*0.737*
AX-In	1.03	(0.88, 1.19)	*0.740*	1.05	(0.88, 1.25)	*0.570*
AX-Control	0.95	(0.81, 1.11)	*0.507*	0.94	(0.80, 1.11)	*0.480*
Cook-C	1.11	(0.97, 1.28)	*0.111*	1.09	(0.94, 1.27)	*0.236*
PTSD	1.10	(0.89, 1.36)	*0.362*	1.13	(0.90, 1.41)	*0.292*
CESD	1.24	(1.11, 1.39)	*<0.001*	1.26	(1.11, 1.43)	*<0.001*
SF12	1.45	(1.32, 1.59)	*<0.001*	1.42	(1.29, 1.58)	*<0.001*
Support-Emotional	0.91	(0.83, 0.99)	*0.044*	0.89	(0.81, 0.99)	*0.030*
Support-Instrumental	0.90	(0.83, 0.97)	*0.008*	0.89	(0.81, 0.97)	*0.009*
Support-Criticism	1.09	(0.99, 1.20)	*0.076*	1.11	(1.01, 1.23)	*0.031*
Support-Isolation	1.15	(1.05, 1.27)	*0.004*	1.17	(1.05, 1.29)	*0.003*
Social Support-Total	0.86	(0.78, 0.95)	*0.002*	0.84	(0.75, 0.93)	*0.001*

Composite CVD	Model A			Model B		
	HR	95% CI	*P-value*	HR	95% CI	*P-value*
PSS	1.06	(0.84, 1.33)	*0.617*	1.06	(0.83, 1.37)	*0.631*
AX-Out	1.06	(0.87, 1.28)	*0.568*	1.08	(0.87, 1.33)	*0.504*
AX-In	1.07	(0.90, 1.28)	*0.420*	1.09	(0.90, 1.31)	*0.382*
AX-Control	1.07	(0.90, 1.28)	*0.438*	1.05	(0.87, 1.28)	*0.583*
Cook-C	1.10	(0.94, 1.30)	*0.238*	1.05	(0.88, 1.25)	*0.595*
PTSD	0.99	(0.82, 1.21)	*0.944*	1.06	(0.86, 1.31)	*0.599*
CESD	1.14	(0.99, 1.32)	*0.064*	1.17	(1.01, 1.36)	*0.041*
SF12	1.15	(1.03, 1.29)	*0.014*	1.11	(0.98, 1.26)	*0.100*
Support-Emotional	0.84	(0.75, 0.94)	*0.003*	0.83	(0.73, 0.93)	*0.002*
Support-Instrumental	0.89	(0.90, 0.99)	*0.037*	0.92	(0.82, 1.04)	*0.181*
Support-Criticism	1.16	(1.03, 1.31)	*0.016*	1.22	(1.07, 1.38)	*0.002*
Support-Isolation	1.18	(1.04, 1.33)	*0.011*	1.15	(1.01, 1.31)	*0.040*
Social Support-Total	0.80	(0.71, 0.90)	*<0.001*	0.79	(0.70, 0.89)	*<0.001*

Notes: Composite cardiovascular disease (CVD), including myocardial infarction, congestive heart failure, stroke. HR= hazard ratio; 95% CI=95% confidence interval. Variables all standardized (z-scored) to allow cross-comparisons. Model A adjustment: field center, age, sex, education, waist-hip ratio; Model B adjustment: Model A plus inflammatory-responsive mediators added, including systolic blood pressure, fasting glucose, C-reactive protein, interleukin 6, plasminogen activator inhibitor 1.

Table 3:

Non-standardized mediation analyses for mortality outcome with social support as mediation features, among American Indians in the Strong Heart Family Study (2001–2003)

Mortality-CESD	Coefficients without medication			Coefficients with mediation			Estimate of % of total effect mediated	
	β	95% CI	P-value	β	95% CI	P-value	%	95% CI
Social-Emotional	−0.09	(−0.11, −0.08)	<0.001	0.02	(0.01, 0.04)	0.002	0.01	(0.01, 0.03)
Social-Instrumental	−0.03	(−0.03, −0.03)	<0.001	0.02	(0.01, 0.03)	0.006	0.09	(0.06, 0.21)
Social-Criticism	0.10	(0.09, 0.11)	<0.001	0.02	(0.01, 0.03)	0.007	0.11	(0.07, 0.25)
Social-Isolation	0.07	(0.06, 0.08)	<0.001	0.02	(0.00, 0.03)	0.014	0.15	(0.10, 0.32)
Mortality-SF12	Coefficients without medication			Coefficients with mediation			Estimate of % of total effect mediated	
	β	95% CI	P-value	β	95% CI	P-value	%	95% CI
Social-Emotional	−0.12	(−0.14, −0.11)	<0.001	0.07	(0.05, 0.09)	<0.001	0.00	(0.00, 0.00)
Social-Instrumental	−0.04	(−0.05, −0.03)	<0.001	0.07	(0.05, 0.09)	<0.001	0.04	(0.04, 0.05)
Social-Criticism	0.14	(0.12, 0.15)	<0.001	0.07	(0.05, 0.09)	<0.001	0.00	(0.00, 0.00)
Social-Isolation	0.09	(0.08, 0.10)	<0.001	0.07	(0.05, 0.09)	<0.001	0.03	(0.03, 0.03)

Logistic regressions of CESD or SF12 on mortality; adjusted for field center, age, sex, education, waist-hip ratio; 1000 replications/simulations