GeroScience (2021) 43:655–672
https://doi.org/10.1007/s11357-020-00319-5

ORIGINAL ARTICLE

The relative contributions of behavioral, biological, and psychological risk factors in the association between psychosocial stress and all-cause mortality among middle- and older-aged adults in the USA

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Received: 22 September 2020 / Accepted: 16 December 2020 / Published online: 28 January 2021

Abstract Evidence of an association between psychosocial stress and mortality continues to accumulate. However, despite repeated calls in the literature for further examination into the physiological and behavioral pathways though which stress affects health and mortality, research on this topic remains limited. This study addresses this gap by employing a counterfactual-based mediation analysis of eight behavioral, biological, and psychological pathways often hypothesized to play a role in the association between stress and health. First, we calculated the survival rate of all-cause mortality associated with cumulative psychosocial stress (high vs. low/moderate) using random effects accelerated failure time models among a sample of 7108 adults from the Midlife in the United States panel study. Then, we conducted a multiple mediator mediation analysis utilizing a counterfactual regression framework to determine the relative contributions of each mediator and all mediators combined in the association between stress and mortality. Exposure to high psychosocial stress was associated with a 0.76 times reduced survival rate over the follow-up period 1995–2015, while adjusting for age, sex, race, income, education, baseline health, and study design effects. The mediators accounted for 49% of this association. In particular, smoking, sedentary behavior, obesity/BMI, and cardiovascular disease displayed significant indirect effects and accounted for the largest reductions in the total effect of stress on mortality, with natural indirect effects of 14%, 12%, 11%, and 4%, respectively. In conclusion, traditional behavioral and biological risk factors play a significant role in the association between psychosocial stress and mortality among middle and older adults in the US context. While eliminating stress and the socioeconomic disparities that so often deliver people into high-stress scenarios should be the ultimate goal, public health interventions addressing smoking cessation, physical activity promotion, and cardiovascular disease treatment may pay dividends for preventing premature mortality in the near-term.

Keywords Adults · Psychosocial · Stress · Mortality

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Introduction

Psychosocial stress, a familiar phenomenon to most, may lead to adverse states of health if exposure becomes excessive and/or chronic in nature. An expansive literature has been generated over the past century demonstrating associations between various measures of psychosocial stress and a multitude of mental and physical health outcomes, including mortality (1–16). However,

less is known about the relative contributions of the hypothesized causal pathways connecting stress to health, especially with regard to mortality (8–12, 17–20). Understanding these causal pathways, as well as their relative contributions, is important for both theory and practice. From a theoretical standpoint, investigating causal pathways aids in testing and revising existing theoretical frameworks, constructing novel theoretical frameworks, and establishing new avenues of research. From a public health perspective, a more precise understanding of causal mechanisms, especially the relative importance of individual pathways, facilitates the design of targeted interventions and efficient use of resources.

Hypothesized causal pathways

The hypothesized causal pathways between psychosocial stress and physical health outcomes, including mortality, can be summarized by three main pathways: (1) biological, (2) psychological, and (3) behavioral. The first two are often referred to as "direct" pathways, whereas the third is generally considered an "indirect" pathway. Each may operate independently or in conjunction with one another. These pathways as well as their interrelationships with one another and other key factors are depicted visually in Fig. S1, a theoretical diagram based on the Reserve Capacity Model developed by Gallo and Matthews (2010).

The biological pathway refers to the pathophysiological changes that occur in response to stress exposure. While the physiological response to acute stress—a process known as *allostasis* —can be beneficial in the near-term (e.g., by providing additional energy and mental acuity for effectively managing a given stressor), it can become detrimental over time through chronic exposure (21–23). Prolonged or repeated exposure to stress and the corresponding activation of the body's stress response systems (i.e., the hypothalamic pituitary adrenal (HPA) axis and the sympathetic adrenal medullary (SAM) system) may result in biological "wear and tear"—or *allostatic load* (23–36). As allostatic load accumulates within the body over time, stress response systems may become dysregulated, perpetuating inflammatory processes and the development of various diseases including cardiovascular disease, diabetes, inflammatory diseases, influenza, and some cancers (30–40). Exposure to chronic stress may also increase one's risk of developing negative mental health outcomes, including depression, anxiety, and chronic sleep problems (27, 37–39). Mental health conditions are in turn associated with increased risk of adverse physical health conditions and mortality. Physical health outcomes, including mortality, may also be influenced indirectly through the adoption of unhealthy coping behaviors, such as alcohol consumption, cigarette smoking, substance use, unhealthy diet, and sedentary activity (14, 22, 40–53).

Existing evidence on hypothesized causal pathways

Biological pathway Stress has been linked to biological, psychological, and behavioral measures through a number of experimental and observational studies (1–4, 20, 27–30, 54–56). Experimental studies have been especially important for studying the complex sequence of biological changes that occur during and immediately following stress exposure. For example, a review of experimental stress test studies found that exposure to an acute stressor was associated with activation of the HPA axis (as measured by cortisol, adrenocorticotropic hormone, vasopressin, and dehydroepiandrosterone), activation of the sympathetic-adrenal-medullary system (measured by adrenaline and noradrenaline), changes in immune activity (observed through increased release and concentration of pro-inflammatory markers) (including IL-6, lymphocytes, monocytes, neutrophils, basophils, granulocytes, T cells, T helper cells, and natural killer cells), cardiovascular stimulation (heart rate peak and variability), changes in mood (reduced calmness, increased anxiety), and cognitive perturbations (memory, task-switching, dual task performance, cognitive flexibility, creativity, choice between present and future rewards, answering questions requiring estimation, strategizing, making decisions involving risk, and assessing risk-taking behavior) (56). However, it is also worth noting that there may be considerable variation in reactivity to such experimental stress tests, with studies observing heterogeneities by age, gender, personality, health, genetics, culture, and other factors (55–60).

Psychological pathway Experimental and observational studies have also demonstrated associations between stress and mental health (37, 61). For example, massive meta-analyses of published and unpublished European cohort studies with over 100,000 participants found that job strain, job insecurity, and unemployment were each associated with a 20–30% increased risk of depressive

symptoms (37, 61). Studies have also shown an increased risk of depression, anxiety, and other emotional problems in response to early life trauma, stressful life events, discrimination, and perceived stress (34, 54, 62–65). Additionally, stress has been correlated with various types of sleep problems. For example, stressful life events were found to be associated with variability in sleep duration, sleep fragmentation, and disrupted circadian cycles (58, 66).

Behavioral pathway Lastly, a number of studies have also shown correlations between stress and various health-related behaviors (14, 20–22, 40–51, 66–69). Psychosocial stress may influence health-related behaviors through a number of possible mechanisms. For example, some behaviors, such as licit or illicit substance use (including alcohol and tobacco) or consuming unhealthy foods (e.g., calorie-rich "comfort foods"), may act as coping mechanisms that aim to placate the pain and discomfort associated with experiences of stress. Exposure to stress may also affect behavior through alterations of the biological systems described above. For example, studies have shown that chronic stress-induced dysregulation of the HPA axis can increase appetite-related hormones (e.g., leptin and ghrelin), promote acquisition of food reward, escalate intake of high fat diets, stimulate compulsive food seeking of palatable foods, and promote reward-dependent habits—ultimately leading to increased consumption of energy-dense calories and substance use including alcohol and tobacco (67–73). Increased consumption of drugs or high fat diets may then lead to an increased sensitization of reward pathways through alterations of corticotropin-releasing factor, glucocorticoids, and noradrenergic activity, thereby perpetuating a feedback loop marked by craving and consumption of addictive substances and high fat foods (67–73)..

Indeed, stress has been associated with substance use, relapse, and addiction in a number of experimental and observational studies (46–48, 70–75). A recent series of massive meta-analyses have shown that job strain is associated with an increased risk of physical inactivity, alcohol consumption, smoking, and the co-occurrence of multiple health-related behaviors (45–47, 74, 76). For example, a meta-analysis of 15 European cohort studies with 166,130 individuals found that individuals exposed to job strain were more likely to smoke and smoke slightly more cigarettes than those not exposed (47). Similarly, a nationally representative study within the USA found that persistent high stress was associated with increased odds of smoking and failure to quit smoking (77). Likewise, a cross-sectional meta-analysis of 12 European studies with 142,140 participants found that job stress was correlated with being a heavy drinker and non-drinker, although further examination of the longitudinal stress-alcohol consumption relationship with the same data produced inconclusive findings (46). Multiple observational studies have found positive associations between various stressors and BMI, weight gain, and obesity (49, 73–75, 78–80). One notable exception is a major meta-analysis of eight cohort studies including 18,240 individuals, which found no significant association between job strain and the risk of becoming obese or gaining weight (76). However, as noted in many of these studies, stress-behavior relationships may be complex and vary by numerous individual attributes, context, stress type, and study design (79, 81). For example, people with preexisting overweightness may be more vulnerable to the behavioral and biological responses associated with stress. A study examining the effects of job strain using data from the Whitehall II study found that men with low bodyweight at the start of the study tended to lose weight over the follow-up period in response to stress, while men with high bodyweight at baseline tended to gain weight (76). Some have hypothesized that higher insulin levels may be partly responsible for the tendency of heavier individuals to gain weight in response to stress (82). Lastly, the behavioral, biological, and psychological effects of stress may also interact with one another. For example, stress-related changes in physical activity, diet, and substance use may exacerbate the adverse effects of stress on immune function or depression. In turn, stress-related depression or physical illness may further amplify the adoption of sedentary behavior, unhealthy eating, or substance use (83).

Study objectives

Although there are robust, albeit not completely understood, associations between stress and behavioral, psychological, and biological risk factors, and between each of these risk factors and mortality, very few studies have explicitly examined the relative contributions of such risk factors in the association between stress and mortality within the same dataset while simultaneously accounting for each of the other risk factors. Therefore, this study seeks to expand on the current literature by

quantifying the relative importance of a number of biological, psychological, and behavioral pathways in driving the association between stress and mortality. Until now, only a single study has examined the role of mediating factors on the association between stress and mortality; however, this study was conducted in a Dutch sample (84). It is therefore important to replicate the findings in a US sample as associations and pathways may vary by context. Some studies have examined stress pathways for health outcomes besides mortality; however, the majority of these relied on more traditional approaches to mediation analysis, such as calculating the difference in the estimate of the main association before and after adjustment for hypothesized mediators. This approach may be useful for testing the hypothesis of the presence or absence of a mediation effect, but often produces biased quantitative estimates of the proportion mediated, especially in more complex study designs, such as survival analysis, the presence of interactions, and the simultaneous examination of multiple mediators (85). Thus, the present study will build on this foundational work by utilizing a counterfactual regression approach to multiple mediation analysis to determine whether a multi-dimensional measure of cumulative psychosocial stress affects all-cause mortality over a 20-year follow-up period, and the extent to which this association is mediated by behavioral (smoking, alcohol consumption, physical activity, substance use), biological (cardiovascular disease, BMI), and psychological (depression, sleep problems) risk factors, in a large, nationally representative sample of midlife adults in the USA.

Methods

Study population

Data for this study derive from the Midlife in the United State (MIDUS) study, a nationally representative panel survey of 7108 non-institutionalized American adults designed to examine the influence of social, psychological, and behavioral factors on health. Participants were recruited into the study from January 1995 to April 1996 via random digit dialing, and surveys were conducted using both telephone and self-administered, mail-in surveys. Among the 7108 participants, 728 are siblings, 1477 are twins, and 488 derive from city-specific oversamples. Longitudinal follow-up surveys were conducted in 2004–2005 (wave 2), and again in 2014–2015 (wave 3), with response rates of 76% and 74%, respectively. Exposure, mediator, and confounder variables for this study were all derived from baseline data from MIDUS 1 (1995/1996) in order to maximize the sample size available for analysis. Mortality data was derived from MIDUS 2 and 3 and corresponded to years covering the period of MIDUS waves 1–3 (1995 to 2015), in order to maximize the length of follow-up time for use in survival models. Multiple imputation (MI) was utilized to account for missingness among independent variables, yielding an analytic sample size of 7108 participants. Further information on the multiple imputation methods used is described below.

Outcome measure: all-cause mortality

All-cause mortality data for this study was obtained as part of MIDUS 2 and MIDUS 3 projects, who originally collected mortality data from National Death Index reports and household proxy reports. Year of death covered the entire study period from 1995 to 2015. Survival time was calculated as the difference between the month of death or last completed survey and the month in which the baseline survey was completed (1995–1996). Participants who were still alive at the end of wave 3 (censored observations) had survival times equal to the length of follow-up (a maximum of 240 months).

Explanatory variable: cumulative psychosocial stress

In order to construct a robust, multi-domain measure of psychosocial stress, we constructed an eight-domain cumulative stress measure based on the scale used by Slopen et al. (77). The cumulative psychosocial stress score was calculated as the standardized sum of eight standardized stress domains, each composed of a sum of a varying number of stress-related subscales, which were themselves the sum of a varying number of individual survey questions. The eight subdomains of stress included relationship stress, financial stress, work stress, work- family spillover, perceived inequality, neighborhood stress, discrimination, and past-year family problems. *Relationship stress* consisted of four measures: family strain, friend strain, marital risk, and spouse/partner strain. *Financial stress* was composed of four individual survey items: current financial situation,

control over finances, enough money to meet needs, and difficulty of paying bills. *Occupational stress* consisted of five measures: job demands, lack of decision autonomy, co-worker non-support, supervisor non-support, and job insecurity. *Neighborhood stress* was composed of three measures: neighborhood disorder, neighborhood distrust, and a lack of neighborhood safety. *Spillover stress* was assessed through two measures: work-to-family spillover and family-to-work spillover. *Past-year family problems* measured the extent to which participants' spouse, children, or parents had to deal with financial, health, legal, relationship, or other demanding "life" problems. *Perceived inequality* assessed whether and to what extent participants were displeased with their experiences or relative position within work, home, neighborhood, and ability to provide for their family. *Discrimination* consisted of two subscales, lifetime discrimination and everyday discrimination, each capturing a different time frame regarding participants' feelings of being discriminated against due to race, ethnicity, gender, religion, sexual orientation, age, physical appearance, or other characteristics across a host of life situations, including work, school, stores, social interactions, and other scenarios. A detailed summary of the individual survey items, subscales, and stress domains used to calculate the cumulative stress scale is provided in Supplementary Materials Table S7. As shown in Slopen et al., each of these stress domain and their corresponding subscales have good reliability (Chronbach's Alpha ranging from 0.69 to 0.97), and many of the subscales have been used extensively in the literature (45, 64, 69, 77)..

Stress subdomains were calculated by summing together the standardized *z*-scores of each subscale corresponding to a specific subdomain. The eight stress domains were then standardized and summed together to yield the cumulative stress score. Cumulative stress was then categorized into a binary variable, where values less than the third quartile were given a value of 0 (low/moderate stress) and values equal to or greater than the third quartile were given a value of 1 (high stress). If a given stress measure was not applicable (e.g., work stress for unemployed participants or marital stress for single participants), the participant was assigned the lowest value for that specific measure (generally a value of 0). As discussed in Supplementary Materials, this measure of cumulative psychosocial stress is found to display good reliability and validity.

Hypothesized mediators

Smoking Smoking was inferred from a single, self-report question: "How many cigarettes do you smoke per day", where non-smokers and ex-smokers received values of 0. Cigarettes per day were then standardized to facilitate comparison with other mediators.

Alcohol consumption Participants were asked about their alcohol consumption behavior on the self-administration portion of the baseline survey via the following questions: "During the year you drank most, about how many drinks would you usually have on the days that you drank?" and "Think about the one year in your life when you drank most. During that year, how often did you TYPICALLY had [sic] at least one drink?" The first question yielded continuous responses, while the second question prompted respondents to select one of the following options: "every day", "5 or 6 days a week", "3 or 4 days a week", "1 or 2 days a week", "less than one day a week", or "never drink". These responses were re-coded to 7, 5.5, 3.5, 1.5, 0.5, and 0, respectively. The re-coded alcohol frequency question was then multiplied by the original alcohol amount/day question and again by 52 to yield the total number of drinks per year. This variable was then standardized in order to enable comparison with other mediators.

Physical inactivity Physical activity was assessed through the following four questions from the self-administered survey: "During the summer, how often do you engage in MODERATE physical activity (for example, bowling or using the vacuum cleaner)?", "What about during the winter – how often do you engage in MODERATE physical activity?", "During the summer, how often do you engage in VIGOROUS physical activity (for example, running or lifting heavy objects) long enough to work up a sweat", and "What about during winter – how often do you engage in VIGOROUS physical activity long enough to work up a sweat?". Response options were as follows: 1 = "several times a week or more", 2 = "about once a week", 3 = "several times a month", 4 = "about once a month", 5 = "less than once a month", and 6 = "never". These four questions were then summed together and standardized to yield a physical inactivity summary variable, such that higher scores corresponded to less frequent bouts of physical activity per month over an entire year.

Substance use Participants were queried on their use of a number of different illegal drugs within the past 12 months, including nerve pills, stimulants, prescription painkillers, inhalants, marijuana, cocaine, LSD, and heroin. An affirmative response to any of the listed illegal substances corresponded to a score of 1 for that question, with a value of 0 given otherwise. The twelve binary variables were then summed together to give the total number of different types of illicit substances used within the past year, which was then standardized to facilitate comparison with other hypothesized mediating variables.

Cardiovascular symptoms Cardiovascular symptoms were assessed using a four-item scale capturing both current and underlying cardiovascular problems, including "Have you ever had heart trouble suspected or confirmed by a doctor [within the past 12 months]?" (0/1), "Have you been diagnosed or given medication for high cholesterol within the past 12 months" (0/1), "Have you been diagnosed or given medication for high blood pressure within the past 12 months?" (0/1), and "How would you describe your current blood pressure" (0 = low/normal, 1 = moderately high, 2 = high, 3 = very high). The scale includes both current blood pressure and a question on the use of blood pressure medication to capture those with high blood pressure problems but who may have experienced a reduction in their blood pressure through the use of medication. The final scale score was standardized to enable comparison across mediators.

Body composition Body composition was measured through self-report questions on both BMI and waist-hip-ratio (WHR). We utilized a WHR-adjusted measure of BMI based on prior research indicating that this approach was more predictive of underlying pathology. This variable was calculated as the standardized sum of standardized WHR and standardized BMI.

Depressive symptoms Participants were asked the following eight, binary questions to ascertain whether they were currently experiencing depressive symptoms disorders: "During the past 12 months, was there ever a time when you felt sad, blue, or depressed for two weeks or more in a row?", "During two weeks in past 12 months when you felt sad, blue, or depressed, did you lose interest in most things?", "During two weeks in past 12 months when you felt sad, blue, or depressed, did you feel more tired out or low on energy than is usual?", "During two weeks in past 12 months when you felt sad, blue, or depressed, did you lose your appetite?", "During two weeks in past 12 months when you felt sad, blue, or depressed, did you have more trouble falling asleep than usual?", "During two weeks in past 12 months when you felt sad, blue, or depressed, did you have a lot more trouble concentrating than usual?", "During two weeks in past 12 months when you felt sad, blue, or depressed, did you feel down on yourself, no good, or worthless?", and "During two weeks in past 12 months when you felt sad, blue, or depressed, did you think a lot about death?". These questions were summed together and standardized to yield a continuous, comparable measure of depressive symptomology.

Sleep problems The frequency of chronic sleep problems was assessed by averaging the following two questions: "In the past 30 days, have you had trouble falling asleep", and "In the past 30 days, have you had trouble waking up at night". Both questions had the same response options: 0 = never, 1 = some days, 2 = most days, and 3 = almost every day. The mean was then standardized to facilitate comparison with other mediators.

Covariates

All models adjusted for baseline age, sex, race, socioeconomic status, and self-reported health in order to control for possible confounding of the stress-mortality associations. Sex was measured as a binary variable (0 = male, 1 = female). Race was measured as a four-level categorical variable (0 = white, 1 = black, 3 = Hispanic/Latino, 4 = other). Socioeconomic status was measured using individual income and participant's highest completed level of education. Self-reported derived from the question "How would you rate your current physical health?" with responses ranging from 1 = "poor" to 5 = "excellent".

Statistical analysis

The primary analytic objective of this study was to estimate the extent to which each of the hypothesized behavioral, biological, and psychological mediators (smoking, alcohol consumption, physical inactivity, substance use, chronic sleep problems, depression, body composition, and cardiovascular disease) mediated the

association between cumulative psychosocial stress and all-cause mortality while adjusting for a number of baseline confounders (age, sex, race, socioeconomic status, and pre-existing health conditions) of the stress-mortality and mediator-mortality associations. We employ a counterfactual regression framework guided by path analysis DAGs and prior research to inform the structure of the models. This approach overcomes the limitations of traditional mediation methods by articulating confounding control assumptions and producing unbiased estimates of direct and indirect effects, even in the presence of multiple mediators, exposure-mediator interaction, and complex designs such as survival analysis (85, 86).

The outcome, time to death, was modeled using accelerated failure time (AFT) models with a Weibull distribution. Accelerated failure time models were chosen because they have been shown to perform better than Cox proportional hazard (PH) regression models in causal mediation analysis settings with non-rare outcomes (> 10%) (85–90). In particular, in settings with non-rare outcomes (like the present study with mortality = 17%), using proportional hazard models with either the product method or difference method will yield invalid estimates of direct and indirect effects, whereas utilizing AFT models with the product method will yield valid estimates (85–90). Further, AFT models offer additional advantages over PH models in general. For example, compared to PH models, AFT models have more intuitive coefficients, represented as the direct effect of an exposure on survival time, are more robust to departures of model assumptions, and may lead to more efficient parameter estimates (91, 92). The Weibull distribution was selected from a set of six possible distributions available for the AFT model by comparing AICs and conducting likelihood ratio tests. Moreover, the Weibull distribution is shown to be a good fit to the data by diagnostic graphical testing (details on model selection and testing provided in Supplementary Materials).

To achieve the analytic objective described above, we first described the distribution of all study variables using summary statistics and summarized the bivariate associations between cumulative stress and each of the hypothesized mediators, potential confounders, and mortality. Second, age, sex, race, income, education, and baseline health-adjusted associations between cumulative stress and standardized versions of each of the hypothesized mediators were estimated using a separate linear regression model for each mediator. Third, age, sex, race, income, education, and baseline health-adjusted associations between standardized versions of each of the hypothesized mediators and mortality were estimated with separate AFT models. Fourth, we estimated the total, direct, and indirect effects of cumulative stress on mortality utilizing a single AFT outcome model and a series of linear regression mediator models, each of which adjusted for age, sex, race, socioeconomic status, pre-existing health conditions, and study design effects.

The outcome model initially took the following general form: $\log[E(T|x,m,c)] = \theta_0 + \theta_1 x + \theta_2 m + \theta_3 xm + \theta_4 c + \sigma\varepsilon$, where x corresponds to the primary exposure, cumulative stress, m captures the set of mediators, c is a vector of confounders, σ describes the Weibull distribution scale and shape parameters, and ε symbolizes the errors, which are assumed to be independent and identically distributed following an extreme value distribution (85, 93). However, after evaluation of the interaction term, θ_3, revealed the absence of any exposure-mediator interaction, the outcome model was reduced to: $\log[E(T|x,m,c)] = \theta_0 + \theta_1 x + \theta_2 m + \theta_4 c + \sigma\varepsilon$. The process of estimating the outcome model with all of the mediators included together in the same model adjusts for possible correlation between mediators. We then fit eight separate mediator models with the following structure: $E(M|x,c) = \beta_0 + \beta_1 x + \beta_2 c + \varepsilon$, where M represents one of eight standardized mediators and x and c again represent the exposure and confounders, respectively. Lastly, all models made adjustment for sibling correlation via cluster robust standard errors and for differences in the probability of selection and differential non-response by the inclusion of sampling weights.

Provided that no-confounding assumptions hold, the statistical models are correctly specified, and variables are without measurement error; these models yield the counterfactual-based natural direct effect (NDE) and natural indirect effect (NIE) of stress on mortality as follows: $NDE = e^{\left[\left\{\theta_1+\theta_1\left(\beta_0+\beta_1+\beta_2+\theta_2\sigma^2\right)\right\}(x-x^*)+0.5\theta_3^2\sigma^2\left(x-x^{*2}\right)\right]}$, $NIE = e^{\left[(\theta_2\beta_1+\theta_3\beta_1 x(x-x^*)\right]}$, where x is high stress and x^* is low/moderate stress. Under the condition of no exposure-mediator interaction, which was observed in the present analysis, the above equations for natural direct and indirect effects reduce to $\theta_1(x-x^*)$ and $\beta_1\theta_2(x-x^*)$, respectively. These are in fact equivalent to the direct and indirect effects estimated from the

product method, or path analysis, approach to mediation (85). The standard errors for the natural indirect effects were calculated using analytic expressions provided by VanderWeele and Vansteelandt for the dichotomous outcome setting (94). Specifically, the standard error of an indirect effect for a dichotomous outcome with a continuous mediator is defined as $\sqrt{(\theta_2+\theta_3 a)^2\sigma_{11}^{\beta}+\beta_1^2\left(\sigma_{22}^{\theta}+2\sigma_{23}^{\theta}a+\sigma_{33}^{\theta}a^2\right)}$, where σ_{ij}^{θ} is the covariance between θ_i and θ_j in the above equation for the NIE. Again, as no exposure-mediator interaction was observed in this study, the standard error equation reduces to $\sqrt{\theta_2^2\sigma_{\beta_1}+\beta_1^2\sigma_{\theta_2}}$. Standard errors obtained from this formula were used in the calculation of confidence intervals for both indirect effects and proportion mediated. To get estimates of the proportion mediated by each mediator, we used the following proportion-mediated measure for direct and indirect effects on the odds ratio scale: $\frac{OR^{NDE}\ X\ \left(OR^{NIE}-1\right)}{OR^{NDE}\ X\ OR^{NIE}-1)}$ (85). Total proportion mediated was calculated as the product of the odds ratio for each of the individual indirect effects. This method assumes parallel mediation and does not account for the possibility of serial mediation—i.e., that any part of the association between a mediator and mortality flows through any of the other mediators (84).

Lastly, as previously mentioned, all analyses were conducted with multiply imputed datasets to account for missing. We chose to construct 20 imputed datasets based on Bodner's rule of thumb suggesting the number of imputed datasets match the percentage of missing data (< = 22% in this study), and evidence from simulation studies showing high relative efficiency with < 1% low preventable power falloff with m = 20 for missing at 30% (95–98). Multiple imputation was conducted using the R "mice" package, which generates multivariate imputations by chained equations. Based on current recommendations for MI, variables chosen for the multiple imputation model included all variables used in the analysis, including the dependent variable, independent variables, combinations of variables (e.g., exposure-mediator interaction terms), and all constituent variables used to construct scales, indexes, or combined variables of any kind (e.g., individual items used to construct the cumulative psychosocial stress measure), for a total of 305 variables (98–100). Further details on imputation methods used in this study are provided in the Supplementary Materials section. All data preparation, imputation, and statistical analyses were conducted in R.

Analytical assumptions

As discussed in the causal mediation analysis literature, identification assumptions for mediation analyses are stronger than for analyses just examining exposure-outcome associations (85, 86, 101–104). In particular, the mediation analysis described above assumes: (1) no exposure-outcome confounding, (2) no exposure-mediator confounding, (3) no mediator-outcome confounding, and (4) no exposure-caused confounding. Furthermore, we make the additional assumptions that there are no exposure-mediator interactions or mediator-mediator interactions. Lastly, we assume that each of the study variables is measured without measurement error. In addition to the mediation-specific assumptions described above, we also make the usual model assumptions regarding model fit for the AFT outcome model and each of the linear regression mediator models. Specifically, we assumed that the AFT outcome model is correctly specified and that the outcome, time to death, follows a Weibull probability density function. Lastly, we assumed that the missing data in our sample are missing at random (MAR) in order for model estimates based on multiply imputed data to remain unbiased.

We tested each of these analytical assumptions whenever possible and conducted sensitivity analyses for those we was unable to test directly. Details of the assumptions testing methods and results are provided in the Supplementary Materials section, but an abridged version is given below. AFT model assumptions were tested graphically with a log-log plot, quantile-quantile plot, and a density plot of time to death overlaid with the theoretical Weibull distribution. Model fit was assessed with Chi-square goodness of fit statistics. The exposure-mediator interaction assumption was assessed via interaction terms and also by decomposition of joint effects—due to the conservativeness of tests of significance for interaction terms.

Sensitivity analyses

For assumptions I–IV, which cannot be assessed directly, we conducted sensitivity analyses to assess the robustness of our results to varying degrees of unmeasured confounding. In particular, we used a bias formula to adjust observed estimates of total, direct, and indirect effects according to unmeasured confounding of

Table 1 Distribution of study variables from the midlife in the united states study for the total sample and by cumulative psychosocial stress

	Total (*N*=7108)	Low stress (*N*=5352)	High stress (*N*=1756)	
	N (%) or mean (SD)	*N* (%) or mean (SD)	*N* (%) or mean (SD)	*P* value
Death	1237(17%)	951 (18%)	286 (16%)	0.1660
Age (years)	46.41(13)	47.5 (13.12)	43.13 (12.06)	<0.001
Sex				
Men	3439 (48%)	2662 (50%)	777 (44%)	<0.001
Women	3669 (52%)	2669 (50%)	1000 (56%)	
Race				
White	6358 (89%)	4911 (92%)	1447 (81%)	<0.001
Black	421 (6%)	230 (4%)	191 (11%)	
Other	329 (5%)	190 (4%)	139 (8%)	
Individual income (dollars)				
<$15,000	2848 (40%)	2048 (38%)	800 (45%)	<0.001
$15,001–$30,000	1220 (17%)	865 (16%)	355 (20%)	
$30,001–$50,000	1428 (20%)	1061 (20%)	367 (21%)	
>$50,000	1612 (23%)	1358 (26%)	254 (14%)	
Participant's highest education				<0.001
<HS	681 (10%)	464 (9%)	217 (12%)	
HS or GED	2060 (29%)	1547 (29%)	518 (30%)	
Some college	2173 (31%)	1592 (30%)	588 (34%)	
≥College graduate	2181 (31%)	1749 (33%)	433 (25%)	
Self-reported health				<0.001
Poor	73 (1%)	48 (1%)	25 (1%)	
Fair	169 (2%)	107 (2%)	62 (4%)	
Good	782 (11%)	532 (10%)	252 (14%)	
Very good	1951 (28%)	1421 (27%)	534 (30%)	
Excellent	4126 (58%)	3244 (61%)	883 (50%)	
Cigarette smoking				
Smoked cigarette in past year	1629 (23%)	1118 (21%)	511 (29%)	<0.001
Cigarettes smoked per day	6.2 (13.3)	5.5 (12.6)	8.2 (15.1)	<0.001
Alcohol consumption (drinks/month)	13.1 (23.9)	12.0 (21.8)	16.3 (29.1)	<0.001
Physical inactivity (days/month)	14.7 (5.0)	14 (4.8)	15 (5.2)	<0.001
Substance use				
Any illicit substance use	1014 (14%)	629 (12%)	385 (22%)	<0.001
Number of illicit substances used	0.23 (0.69)	0.17 (0.57)	0.39 (0.93)	<0.001
Cardiovascular symptoms scale	3.19 (0.9)	3.17 (0.9)	3.25 (1.0)	<0.001
Body composition				<0.001
BMI	26.7 (5.3)	26.4 (4.8)	27.6 (6.3)	<0.001
WHR	0.88 (0.1)	0.88 (0.1)	0.88 (0.1)	0.887
Depressive symptoms scale	0.8 (1.9)	0.6 (1.7)	1.4 (2.4)	<0.001
Sleep problems (episodes/month)	2.42 (1.7)	2.25 (1.6)	2.93 (1.8)	<0.001

All behaviors refer to the past 12 months, unless stated otherwise

HS high school, *GED* general educational development, *BMI* body mass index, *WHR* waist hip ratio

varying severities, also calculating the precise extent of confounding needed to completely eliminate each of the observed associations. We also examined the degree to which our findings changed as a function of measurement error by substituting alternate exposure and mediator measures.

Results

The analytic sample used in this study consisted of 7108 participants who, at baseline, were an average of 46 years old (range: 20–75), 52% female, 89% white, and predominantly of middle-class backgrounds with a median individual income of between $20,000 and 25,000 per year in 1995 dollars, and 90% having a high school degree or more education (Table 1). One thousand seven hundred seventy-one (25%) participants were classified as high stress, while 5331 (75%) were low to moderate stress. Those in the higher stress group tended to be younger, were more likely to be women, were less likely to be white, had lower individual incomes, and were more likely to report worse physical health at baseline. Furthermore, those who reported greater stress were more likely to engage in unhealthy behaviors and experience adverse states of mental and physical health. There also tended to be greater variance in measures of health behaviors and adverse states of physical and mental health in the high-stress group compared to the low/moderate stress group (Table 1).

Table 2 Associations between standardized behavioral, biological, and psychological risk factors and all-cause mortality (n = 7108)[a]

Risk factors (standard deviations)	Survival rate (95%CI)
Cigarette smoking	0.78 (0.74, 0.82)***
Alcohol consumption	0.95 (0.90, 0.99)**
Physical inactivity	0.87 (0.85, 0.89)***
Substance use	0.94 (0.89, 0.99)*
Cardiovascular symptoms scale	0.90 (0.86, 0.95)***
WHR-adjusted BMI	0.88 (0.81, 0.94)***
Depressive symptoms scale	0.94 (0.89, 1.00)†
Sleep problems	0.95 (0.90, 0.99)*

[a] Survival rates calculated from separate accelerated failure time models adjusting for age, sex, race, income, education, self-reported health, sampling weights, and sibling clustering. $^{\dagger}p < 0.10$, $^{*} < 0.05$, $^{**} < 0.01$, $^{***} < 0.001$

In models adjusting for demographic factors, socioeconomic status, and baseline health, those in the high-stress group had higher levels of smoking, alcohol consumption, substance use, sedentary behavior, cardiovascular symptoms, WHR-adjusted BMI, depressive symptoms, and sleep problems compared to those in the low- to moderate stress group (Table 2).

Over the follow-up period from 1995 to 2015, 1237 (17.4%) study participants died. Participants in the high-stress group had a lower survival rate than those in the low-/moderate stress group. Results from accelerated failure time model adjusting for sociodemographic factors, baseline health, and study design effects indicated that membership in the high-stress group is associated with a 22% reduced survival rate (SR = 0.74, 95%CI: 0.68, 0.90) (Table 3). Since the AFT model was specified using a Weibull distribution, parameter estimate for log-survival time may also be interpreted in terms of hazards ratios (HR) with a transformation utilizing the scale parameter, σ, i.e., $e^{-1*\beta_1/\sigma}$. (93) Following this procedure yielded a HR of 1.46 comparing the high- to low-/moderate stress groups. Each of the hypothesized mediators was also associated with mortality. Specifically, in adjusted AFT models, smoking was associated with a 23% reduced survival rate, alcohol consumption was associated with a 7% reduction in survival, physical inactivity reduced survival by 14%, substance use by 6%, cardiovascular symptoms by 10%, BMI by 14%, sleep problems by 6%, and depressive symptoms by 6% (Table 3).

Results from the multiple mediator mediation analysis (Table 4 and Fig. 1) reveal a substantial attenuation of the stress-mortality association. In particular, taken together, the eight behavioral, biological, and psychological mediators accounted for 70% of the total effect of stress on mortality and reduced the magnitude of the SR from 0.78 (95%CI: 0.68, 0.90) to 0.87 (95%CI: 0.73, 1.03). Individually, cigarette smoking, physical inactivity, cardiovascular symptoms, and BMI accounted for the majority of the mediation and were the only mediators with significant indirect effects. Depression, sleep problems, substance use, and alcohol consumption demonstrated positive, but non-significant indirect effects. Specifically, smoking accounted for 17% of the association between stress and mortality, BMI accounted for 17%, physical inactivity accounted for 16%, and cardiovascular symptoms accounted for 6%.

Table 3 Associations between cumulative psychosocial stress and standardized behavioral, biological, and psychological risk factors (n = 7108)[a]

	Smoking	Alcohol	Phys. Inactivity	Substance use	CVD [b]	BMI [b]	Depression	Sleep
Stress	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
High	0.15 (0.10, 0.20)	0.20 (0.14, 0.25)	0.29 (0.24, 0.34)	0.31 (0.25, 0.37)	0.18 (0.12, 0.24)	0.28 (0.23, 0.34)	0.38 (0.33, 0.44)	0.45 (0.39, 0.50)
Low	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[a] Parameter estimates refer to the difference in standard deviations for each risk factor comparing high vs. low stress participants, adjusting for age, sex, race, income, education, pre-existing health, sampling weights, and sibling clustering

[b] *CVD* cardiovascular disease, *BMI* body mass index

Discussion

Summary of findings

In this study, we evaluated the association between cumulative psychosocial stress and all-cause mortality in a nationally representative sample of US adults and quantified the extent to which this association was mediated by behavioral, biological, and psychological risk factors. We observed that cumulative psychosocial stress is associated with a significant 22% reduced survival rate, or 1.42 times greater hazards, for all-cause mortality when comparing participants with high stress to those with low to moderate stress and adjusting for sociodemographic factors, baseline health, and study design effects. Additionally, the combined effect of the eight behavioral, biological, and psychological mediators accounted for 70% of this association, with the majority of the attenuation deriving from smoking, physical inactivity, BMI, and cardiovascular symptoms. In particular, the association between stress and mortality was mediated by 17% from smoking, 17% from BMI, 16% from physical inactivity, and 7% from cardiovascular symptoms.

Table 4 Role of behavioral, biological, and psychological mediators in explaining the association between psychosocial stress and all-cause mortality (n = 7108) [a]

	Total Effect	NDE	NIE	Proportion mediated [b]
	SR (95%CI)	SR (95%CI)	SR (95%CI)	% (95%CI)
	0.78 (0.68, 0.90)***	0.87 (0.73, 1.03)		
All mediators combined				70%
Cigarette smoking			0.97 (0.96, 0.98)***	17% (10%, 23%)
WHR-adjusted BMI			0.97 (0.95, 0.99)**	17% (6%, 26%)
Physical inactivity			0.97 (0.95, 0.99)**	16% (5%, 24%)
Cardiovascular symptoms			0.99 (0.98, 1.99)*	7% (1%, 13%)
Depressive symptoms			0.99 (0.98, 1.03)	5% (−32%, 12%)
Sleep problems			0.99 (0.98, 1.04)	4% (−32%, 14%)
Substance use			0.99 (0.97, 1.02)	3% (−17%, 17%)
Alcohol consumption			1.00 (0.99, 1.01)	1% (−8%, 8%)

[a] Estimates for indirect effects derived from a single outcome model simultaneously accounting for all other mediators and eight individual mediator models. All models adjusted for age, sex, race, income, education, self-reported health, sampling weights, and sibling clustering

[b] Proportion mediated calculated from the equation $(SR_{NDE} * (SR_{NIE} - 1)/(SR_{NDE} * SR_{NIE} - 1)$. $^{\dagger} p < 0.10$, $^{*} < 0.05$, $^{**} < 0.01$, $^{***} < 0.001$

SR survival rate, *NDE* natural direct effect, *NIE* natural indirect effect, *WHR* waist hip ratio, *BMI* body mass index

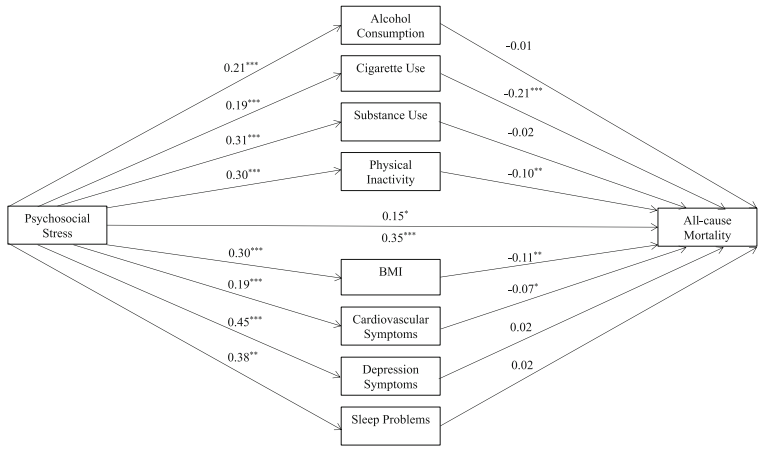

Fig. 1 Diagrammatic representation of the total, direct, and indirect effects of cumulative psychosocial stress on all-cause mortality. Standardized path coefficients estimated from regression models adjusting for age, sex, race, income, education, and self-reported health. $^{\dagger}p < 0.10$, $^{*} < 0.05$, $^{**} < 0.01$, $^{***} < 0.001$

Relationship to existing research

These results are in accordance with and expand upon previous studies investigating stress and mortality. The extant literature on stress and mortality in the USA is mixed, but the majority of evidence thus far supports the presence of a positive association (7–16). The present findings add further evidence in support of this conclusion. Further, the magnitude of the effect of stress on mortality observed here (42% increase) is similar to previous studies, which tended to be around 40% (with a range of 30–90%) among studies finding a significant association. For example, Aldwin, et al. observed a 42% increased risk of mortality in response to stressful life events among a sample of older men in the VA Normative Aging Study (9). Amick et al. saw a 43% increased hazards of mortality among workers exposed to low control jobs in the Panel Study of Income Dynamics (7). And Keller et al. reported a 43% increased risk of mortality among participants from the National Health Interview Study who reported both high exposure to stress and the perception that stress affected their health (13).

Results from this study also expand current evidence on stress pathways. Specifically, this is the first study to quantify the relative contributions of behavioral, biological, and psychological pathways between stress and mortality in a US sample. Compared to a path analysis study conducted in the Netherlands by Rutters et al., our findings are fairly similar (84). In particular, Rutters et al. observed a 1.44 (95%CI: 1.08, 1.92) times greater hazards of all-cause mortality over the 20-year follow-up period among those reporting four or more stressful life events within the past 5 years compared to those reporting none (84). Of the total effect due to stressful life events, 33% was mediated by behavioral and biological risk factors, of which 12% was due to smoking, 9% was from cardiovascular disease, 7% from type 2 diabetes, 4% due to physical inactivity, and 1% from high alcohol consumption. Thus, the relative importance of traditional risk factors such as smoking, cardiovascular disease, and physical inactivity was evident in both studies, as was the null effect for alcohol consumption. Yet, the absolute mediating effect for such risk factors was generally larger in the present. This may be due to a number of factors from methodological discrepancies (e.g., measurement of stress and mediating variables, mediation analysis methods, PH vs. AFT models) to differences in sample (the Dutch sample was composed only of older adults, aged 50–75) and context (the USA vs. the Netherlands). For example, perhaps physical inactivity was a stronger mediator in the present study because Americans are more likely than the Dutch to respond to stress by becoming sedentary, or because there is a tighter relationship between physical inactivity and mortality within the USA. Future studies should conduct similar mediation analyses in order to verify the mediating effects observed by Rutters et al. and the present study.

Strengths and limitations

The results presented in this study expand on the current literature on stress and health by utilizing a comprehensive measure of cumulative psychosocial stress, longitudinal data with 20 years of follow-up, and a large, nationally representative sample. Many past studies on stress and mortality in the US relied on data

from small, clinical trials with limited or otherwise non-representative samples (e.g., older males or cardiovascular disease patients) (11, 12, 105). Further, most of the previous studies investigating stress and mortality relied on single domains of stress (e.g., work stress, stressful life events) or even single item stress measures (7, 9, 11–15, 105). We expanded on these limitations by utilizing a comprehensive measure of cumulative psychosocial stress incorporating multiple domains of the stress experience. Much of the stress literature is also limited to cross-sectional data or longitudinal data with short follow-up time, whereas our study benefited from 20 years of follow-up mortality data. Furthermore, despite repeated calls for examination into the physiological and behavioral pathways though which stress affects health and mortality, research on this topic has remains limited (5, 7, 9, 10, 12–14, 16–18, 64, 106–108). To that end, this was the first US study that we are aware of to explore multiple mediating mechanisms of the stress-mortality relationship. This endeavor is further strengthened by the use of a counterfactual mediation framework coupled with an accelerated failure time modeling approach, which allows for easily interpretable estimates of direct and indirect effects with causal interpretations under the no-confounding conditions described above.

Nonetheless, our study is not without limitations. First, the exposure and mediators were all measured at the same point in time. Thus, it is impossible to say for certain whether the hypothesized pathways are a true representation of reality. That is, it is possible that the variables hypothesized to act as mediators of the stress-mortality association are in fact confounders of this association, either in part or in full. Second, absence of longitudinal data for the mediators also prevents investigation into serial mediation. For example, part of the physical inactivity pathway may act through cardiovascular disease and obesity, or vice versa, but it is impossible to accurately investigate such hypotheses without measurement of each mediator at multiple time points. Third, measures of behavioral, biological, and psychological factors were potentially limited in terms of measurement. The baseline MIDUS survey relied on self-report for all questions, including those regarding behaviors, biological metrics, and health conditions. Future investigations would benefit from objective measures of behaviors, health conditions, and biological markers (e.g., cortisol, blood pressure, cholesterol, etc.), assessed over multiple followups, in order to allow for more thorough mediation analyses. Results from such studies could assist in teasing out the precise role of allostatic load and other mechanisms in driving the relationship between stress and mortality, and their interrelationships with behavioral and psychological pathways. Lastly, the data utilized in the present study arelimited in terms of racial composition, with nearly 90% of the sample composed of non-Hispanic white participants. While this proportion was more representative of the U.S. population during the baseline year of MIDUS (1995), it is less representative of the current (2020) racial composition in the U.S. Hence extrapolations to the broader population may need to be performed with caution.

Future directions

Future studies should aim to replicate the analyses presented here using more diverse samples with longer longitudinal data (over the entire life course if possible) with multiple (and more frequent) measurement time points for all study variables including the exposure, confounders, and mediators (objectively measured whenver possible), and incorporating additional mediating variables. In particular, objectively measured behavioral and biological mediating variables coupled with measurement at multiple time points would allow future studies to develop a more nuanced understanding of the causal pathways connecting stress and mortality. Of particular interest would be examining the bi-directional relationships between behavior and biology and the role of biological dysregulation in these interrelated relationships. It would also be important to know whether these relationships hold for more diverse populations, and whether they vary by individual characteristics (e.g., age, race/ethnicity, and gender), genetics, personality traits, psychosocial resources (e.g., resiliency, social support, and social capital), socioeconomic factors (e.g., income, weatlh, and status), or environmental conditions. Lastly, investigating the extent to which exposure and susceptibility to stress can be mitigated by interventions and whether there are sensitive periods of development suitable for early intervention would be of particular interest for expanding our ability to not only understand but prevent the health costs (including premature morbidity and mortality) associated with psychosocial stress.

Broader implications for public health

The results presented in this study provide preliminary evidence on the relative magnitudes of multiple behavioral, biological, and psychological pathways connecting exposure to psychosocial stress and all-cause mortality within the US. Taken together with existing stress literature, these findings can help guide public health interventions to modulate the adverse effects of stress on population health. For example,short of eliminating stress altogether, public health practitioners may utilize results from this and similar studies to target important stress pathways (e.g., unhealthy coping behaviors, biological processes, and psychological intermediaries) in order to limit the adverse health consequences of stress. Thus, stress prevention interventions—targeting both environmental and individual modifications—should be implemented as part of a broader public health effort including attention to the social, material, behavioral, and biological determinants of disease and mortality.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11357-020-00319-5.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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