



Number of recent stressful life events and incident cardiovascular disease: Moderation by lifetime depressive disorder



Jessica Berntson, Jay S. Patel, Jesse C. Stewart*

Department of Psychology, Indiana University-Purdue University Indianapolis (IUPUI), Indianapolis, United States

ARTICLE INFO

Keywords:

Life change events
Stress, psychological
Depressive disorder
Cardiovascular diseases
Prospective studies
Epidemiologic studies

ABSTRACT

Objective: We investigated whether number of recent stressful life events is associated with incident cardiovascular disease (CVD) and whether this relationship is stronger in adults with a history of clinical depression. **Methods:** Prospective data from 28,583 U.S. adults (mean age = 45 years) initially free of CVD who participated in Waves 1 (2001–2002) and 2 (2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) were examined. Number of past-year stressful life events (Wave 1), lifetime depressive disorder (Wave 1), and incident CVD (Wave 2) were determined by structured interviews.

Results: There were 1069 cases of incident CVD. Each additional stressful life event was associated with a 15% increased odds of incident CVD [Odds Ratio (OR) = 1.15, 95% Confidence Interval (CI): 1.11, 1.19]. As hypothesized, a stressful life events by lifetime depressive disorder interaction was detected ($P = 0.003$). Stratified analyses indicated that stressful life events had a stronger association with incident CVD among adults with (OR = 1.18, 95% CI: 1.10, 1.27, $n = 4908$) versus without (OR = 1.10, 95% CI: 1.07, 1.14, $n = 23,675$) a lifetime depressive disorder.

Conclusion: Our findings suggest that a greater number of recent stressful life events elevate the risk of new-onset CVD and that this risk is potentiated in adults with a history of clinical depression.

1. Introduction

A growing body of evidence supports a prospective relationship between chronic stress in adulthood and an increased risk of developing atherosclerotic cardiovascular disease (CVD) – i.e., clinical conditions that result from atherosclerosis including coronary artery disease (CAD), myocardial infarction (MI), arteriosclerosis, and angina. The majority of these studies have focused on overall perceived stress [1] or specific types of stress, such as work stress [2–5] or relationship stress [5–8]. Fewer studies have examined the prospective link between the number of stressful life events and incident CVD, and the existing results are mixed. In the Multiple Risk Factor Intervention Trial involving only men, annual accumulation of stressful life events was positively associated with incident angina but not incident MI or CAD death [9]. In the Copenhagen City Heart Study, a longitudinal relationship was observed between accumulation of adulthood stressful life events and incident stroke but not incident CAD or MI [10,11]. Finally, in two recent investigations, the Women's Health Initiative which measured past-year stressful life events and the Multi-Ethnic Study of Atherosclerosis which measured ongoing stressful life events with durations

longer than 6 months, stressful life events was associated with both incident CAD and stroke [12–14]. Thus, it remains unclear whether number of stressful life events is associated with incident CVD. Moreover, no study to date has examined the stressful life events-CVD relationship in a large and diverse sample that is sociodemographically representative of the U.S. adult population.

The stressful life events-CVD relationship may be more pronounced in certain groups. Depressed adults may be one such group, as they exhibit altered physiologic and behavioral responses to stressors. First, depressed adults display delayed sympathetic [15], hypothalamic-pituitary-adrenal (HPA) axis [16], cardiovascular [17,18], and inflammatory [19] recovery from laboratory-induced stress, suggesting that depression may interfere with normal homeostatic suppression of these physiologic stress response systems after a stressor has terminated [20]. Indeed, ruminative perseverative cognition is a core feature of depression [21,22], which may contribute to a prolonged stress response across autonomic, endocrine, cardiovascular, and inflammatory systems [23]. Second, depressed adults are more likely than their nondepressed counterparts to engage in poor behavioral strategies to cope with stress [22], such as avoidance-based emotional eating and

* Corresponding author at: Department of Psychology, Indiana University-Purdue University Indianapolis (IUPUI), 402 North Blackford Street, LD 100E, Indianapolis, IN 46202, United States.

E-mail address: jstew@iupui.edu (J.C. Stewart).

<http://dx.doi.org/10.1016/j.jpsychores.2017.06.008>

Received 27 February 2017; Received in revised form 31 May 2017; Accepted 10 June 2017
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substance use [24,25]. In turn, these altered responses to stressors may promote the development and progression of atherosclerosis [20,26,27], thereby potentiating the effect of stressful life events on CVD in depressed adults. However, to our knowledge, no study has investigated whether depression moderates the relationship between stressful life events and incident CVD.

Accordingly, our objectives were to examine whether number of stressful life events is prospectively associated with new-onset CVD and whether depression moderates this relationship in a large sample of American men and women. We hypothesized that (a) number of recent stressful life events would be positively associated with incident CVD and (b) this association would be stronger in adults with versus without a lifetime history of a depressive disorder. We analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a prospective cohort study of a large probability sample representative of the U.S. population. NESARC provided a good opportunity to test our hypotheses, given that this survey included measures of stressful life events and lifetime depressive disorder diagnoses at baseline, as well as clinical CVD at baseline and the 3-year follow-up.

2. Methods

2.1. Study design and sample

NESARC was conducted by the National Institute on Alcohol Abuse and Alcoholism to determine the prevalence of alcohol use disorders and associated disabilities in the U.S. civilian noninstitutionalized population ≥ 18 years [28–30]. NESARC received ethical approval by the U.S. Census Bureau and the U.S. Office of Management and Budget. With involvement of the U.S. Census for sample design and field work, NESARC surveyed a representative sample of the U.S. adult population from counties across the 50 states, oversampling non-Hispanic Black people, Hispanic/Latino people, and young adults aged 18–24 years. Data were weighted to adjust for probabilities of selection, non-response, and oversampling. Weighted data were further adjusted to represent the U.S. civilian population for various sociodemographic variables, including region, age, sex, race, and ethnicity, based on the 2000 Decennial Census. Respondents underwent two waves of face-to-face, computer-assisted, home interviews separated by three years (mean = 36.6 months) assessing substance use disorders, psychiatric disorders, and medical conditions. Wave 1 (2001–2002) consisted of 43,093 respondents (81.0% response rate) and Wave 2 (2004–2005) consisted of 34,653 (86.7%) of the eligible Wave 1 respondents (70.2% cumulative response rate). To the Wave 2 sample, we applied four exclusion criteria. Respondents were excluded if: [1] CVD status at Wave 1 was missing (n = 1719) or positive (n = 1742), [2] CVD status at Wave 2 was missing (n = 1112), [3] stressful life events or lifetime depressive disorder at Wave 1 was missing (n = 196), or [4] any covariates at Wave 1 were missing (n = 1301). Table 1 displays the characteristics of our final sample of 28,583 U.S. adults.

2.2. Measures

2.2.1. Stressful life events

NESARC developed a list of 12 stressful life events by adapting items from two existing measures: the List of Threatening Experiences [31] and the Schedule of Recent Events [31,32]. According to a previous factor analysis, these events fall into one of four stress domains: health, social, job, and legal [33]. During the Wave 1 interview, respondents reported whether or not they had experienced the 12 stressful life events in the past year (see Fig. 1 for the yes-no questions). This one-year recall period is recommended in order to capture a reasonable estimate of variability in event exposure and to avoid substantive decline in the ability of respondents to recall events beyond one year [34]. From the stressful life events data, we computed a continuous stressful life events variable by summing the number of events and merging six

Table 1
Characteristics of sample (N = 28,583).

Age, years, mean (SD)	44.8 (17.0)
Female, %	57.6
Race/ethnicity	
Non-Hispanic White, %	58.2
Non-Hispanic Black, %	18.6
Hispanic or Latino, %	18.7
Other, %	4.5
Education level	
Less than high school, %	15.2
High school or equivalent, %	28.5
Some college or associate's degree	30.6
Bachelor's degree or higher, %	25.7
Hypertension, %	18.1
Hypercholesterolemia, %	19.2
Diabetes, %	8.0
Tobacco use, %	25.6
Body mass index, kg/m ² , mean (SD)	27.0 (5.6)
Number of past-year stressful life events, mean (SD)	1.6 (1.6)
Lifetime depressive disorder, %	17.2
Lifetime major depressive disorder, %	16.4
Lifetime dysthymic disorder, %	3.9
Incident CVD, %	3.7
Incident arteriosclerosis, %	1.2
Incident angina, %	2.6
Incident myocardial infarction, %	0.6

- In the last 12 months...

 1. Did any of your family members or close friends die?
 2. Did any of your family members or close friends have a serious illness or injury?
 3. Did you move or have anyone new come to live with you?
 4. Were you fired or laid off from a job?
 5. Were you unemployed and looking for a job for more than a month?
 6. Have you had trouble with your boss or a coworker?
 7. Did you change jobs, job responsibilities or work hours?
 8. Did you get separated or divorced or break off a steady relationship?
 9. Have you had serious problems with a neighbor, friend or relative?
 10. Have you experienced a major financial crisis, declared bankruptcy or more than once been unable to pay your bills on time?
 11. Did you or a family member have trouble with the police, get arrested or get sent to jail?
 12. Were you or a family member the victim of any type of crime?

Fig. 1. Questions assessing the number of past-year stressful life events at Wave 1 (2001–2002) of the National Epidemiologic Survey on Alcohol and Related Conditions.

or more events into a single category due to sparseness of data at higher values (number of past-year events: 0, 1, 2, 3, 4, 5, or 6+). This approach to constructing a continuous stressful life events variable has been utilized previously with NESARC data [35]. Notably, test-retest correlations for stressful life events checklists are fairly stable (approximate *r* range for test-retest intervals of 6 months or more: 0.4 to 0.7), despite the longer recall period at retest likely reducing respondents recall ability [34].

2.2.2. Lifetime depressive disorder

The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV) was administered by lay interviews at Wave 1 to assess lifetime major depressive disorder and dysthymic disorder [36]. The AUDADIS-IV, a fully structured diagnostic interview based on DSM-IV criteria, has demonstrated good test-retest reliability for depressive disorders and good agreement with clinician evaluations [30,37].

NESARC personnel coded diagnostic variables for the past year or prior to the past year. From the NESARC depression variables that excluded illness-induced and substance-induced disorders and ruled out bereavement [28], we calculated a dichotomous lifetime depressive disorder variable as follows: [1] yes: respondents coded as positive for major depressive disorder or dysthymic disorder in past year or prior to

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