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Ten Surprising Facts About Stressful Life Events and Disease Risk

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Abstract

After over 70 years of research on the association between stressful life events and health, it is generally accepted that we have a good understanding of the role of stressors in disease risk. In this review, we highlight that knowledge but also emphasize misunderstandings and weaknesses in this literature with the hope of triggering further theoretical and empirical development. We organize this review in a somewhat provocative manner, with each section focusing on an important issue in the literature where we feel that there has been some misunderstanding of the evidence and its implications. Issues that we address include the definition of a stressful event, characteristics of diseases that are impacted by events, differences in the effects of chronic and acute events, the cumulative effects of events, differences in events across the life course, differences in events for men and women, resilience to events, and methodological challenges in the literature.

Keywords

stressors; life events; health; disease

INTRODUCTION

Definitions of stress vary in their foci from objective threatening characteristics of the environment—stressful life events—to individuals' (subjective) appraisals of the threat that an environment poses for them—psychological stress—to the activation of physiological systems that support the behaviors (e.g., fight and flight) needed to respond to that threat (Cohen et al. 2016). These varying definitions have been viewed as representing different stages in a model where stressful life events that an individual appraises as threatening trigger behavioral and physiological responses with possible downstream implications for disease (Cohen et al. 2016).

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DISCLOSURE STATEMENT

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In this review, we focus on major stressful life events (also called stressors). Our interest in objectively defined events is partly attributable to a substantial literature associating events with risk for, and exacerbation of, a range of diseases including depression, coronary heart disease (CHD), HIV/AIDS, asthma, autoimmune diseases, respiratory infections, and mortality (for a review, see Cohen et al. 2007), but it is also attributable to our recognition that, from a public health perspective, reducing environmental stressors may be easier and more cost effective than treating individuals' psychological or physiological responses.

We focus on events that are threats to one's social status, self-esteem, identity, or physical well-being, such as divorce, the death of a loved one, the loss of a job, being arrested, retirement, or being diagnosed with a serious illness. Much of what we know about stressful life events is derived from research using major stressful life event checklists (Monroe 2008). These scales assess the number of major events that a person reports experiencing in a defined time span, usually a year, based on the assumption that events are cumulative. That is, each event adds to the total stress burden. In contrast to the assumptions of this approach, there is also substantial evidence for an increased risk for disease among those who have experienced a single event. Most convincing in this regard are studies that identify major threatening events using a structured interview called the Life Events and Difficulties Schedule (LEDS) (Brown & Harris 1989). In this method, the threat of an event is assessed using information garnered from the interview, and the event is rated by comparison to records (a dictionary) of ratings of similar events experienced by others previously interviewed using the LEDS. Individual events that meet a common criterion for threat (the average person would be severely threatened) are thought to be substitutable in their risk for disease, but experiencing multiple events does not increase that risk.

After over 70 years of research on the association between stressful life events and health, it is generally accepted that we have a good understanding of the role of stressors in disease risk. In this review, we highlight that knowledge but also emphasize misunderstandings and weaknesses in this literature with the hope of triggering further theoretical and empirical development. We organize this review in a somewhat provocative manner, with each section focusing on an important issue in the literature where we feel that there has been some misunderstanding of the evidence and its implications.

THE TEN FACTS

Fact 1: There Is Little Agreement on the Characteristics that Define a Stressful Event

There is a consensus among researchers that severe circumstances such as death of a spouse, sexual assault, or learning of a diagnosis of imminent death are examples of major stressful life events—events that we expect will result in psychological and physiological stress responses for the average person. Less clear is what the necessary criteria are for an event to be classified as stressful. In this section, we present four alternative theoretical perspectives on what constitutes a stressful event.

Adaptation.—The first approach views the stressfulness of an event as the amount of adaptation or change it requires of an average individual (Holmes & Rahe 1967). This implies that stressful events are cumulative, with each additional event adding to the overall

burden of change. It also implies that positive events (e.g., marriage, vacations) can also be stressful events if they require substantial adaptation.

Threat or harm.—The second approach defines stressful events as those that are consensually seen as harmful or threatening (e.g., Brown & Harris 1989, Cohen et al. 2016). Imminence of harm, intensity, duration, and the extent to which an event is objectively uncontrollable are all factors that contribute to the potential magnitude of consensual threat (Lazarus & Folkman 1984, Rabkin & Struening 1976). As mentioned above, although the magnitude of the threat represented by different life events is often thought to be cumulative (e.g., as assumed by stressful life event checklists), there is also evidence that the maximum risk for disease occurs when a single event meets a high criterion for threat (Wethington et al. 1995), with additional events not adding to the total risk.

Demands exceed resources.—The third approach arises out of the job stress literature. The underlying assumption is that a demanding situation results in psychological distress and strain when decision latitude and control over characteristics of the situation are insufficient (e.g., Karasek et al. 1981). Although this assumption is borrowed from approaches to psychological stress where psychological demands and control are each subjectively appraised by the individual (Karasek et al. 1981, Lazarus & Folkman 1984), it has also been employed as an objective assessment of job strain through the application of consensual (e.g., the average response of workers with a specific job) or expert (supervisors') ratings of demands and control (Frese & Zapf 1988, Karasek & Theorell 1990).

Interruption of goals.—Finally, the fourth approach defines stressful events as interruptions of major goals (Carver & Scheier 1999), including goals to maintain one's physical integrity and one's psychological well-being (Kemeny 2003, Lazarus & Folkman 1984). This approach is primarily rooted in evidence that interference with personal goals is associated with emotional distress, but it has not been widely studied in the prediction of illness outcomes (Carver & Scheier 1999, Wrosch et al. 2007). Goal interruption is also central to Brown & Harris's (1989) position that threat is primarily rooted in disruption of roles or plans in the context of a person's life goals. Our own view that events are threats to one's social status, self-esteem, identity, and physical well-being may also be folded in to the goal interruption theory, with each of these representing a core goal that is consensually viewed as important.

Which approach is correct?—There is obvious overlap among these approaches. For example, the interruption of goals may occur when demands exceed decision latitude, and goal interruption probably generates both threat and a need to adapt. The adaptation approach has received the most direct testing of its assumptions, with only mixed results. For example, summing of judges' weights of how much change each event on a life event checklist requires is no more predictive of health outcomes than just counting the number of events, and positive events (e.g., marriage, vacation) that require adaptation are unlike negative ones in that they do not contribute to the predictability of life event checklists (Turner & Wheaton 1995).

Overall, the threat or harm approach is the most commonly accepted perspective. There is considerably less evidence addressing the validity of the demands versus control and decision latitude and goal interruption approaches. Moreover, one could argue that these two approaches are merely subsets of the threat approach. The simplicity of the adaptation approach remains attractive (Turner & Wheaton 1995), even though some key hypotheses derived from this perspective have not held up. It is a challenge for future researchers to more clearly distinguish among the sensitivities of these alternative approaches and to delineate any important differences in their predictions for the types of environmental events with the potential to influence our health and well-being.

Fact 2: Stressful Events Can Impact Most Diseases

There are a variety of mechanisms through which the experience of stressful events may influence the onset of clinically defined disease, preclinical or clinical disease progression, or both (Miller et al. 2009). The pathways linking stressful event exposure to disease that have been extensively studied include alterations in affective regulation (e.g., elevated levels of anxiety, fear, depression), health behaviors (e.g., poor nutrition, not exercising, overconsumption of alcohol, smoking cigarettes, poor sleep), and neurohormonal systems (e.g., changes in the output or tissue effects of hormones such as cortisol, testosterone, and estrogen), as well as direct innervation of tissues by the autonomic nervous system (e.g., heightened sympathetic nervous system activity resulting in increased release of norepinephrine). Modification of any of these pathways could potentially result in deleterious changes to major organs (e.g., brain, heart, liver) and bodily systems (e.g., immune, endocrine, and cardiovascular systems) (McEwen 2012). Thus, in theory, exposure to stressful events may impact any disease with an etiology involving affect regulation, health behaviors, hormones, or the autonomic nervous system. This formulation suggests that many diseases or disease processes with multifaceted etiologies may theoretically be subject to modulation by stressor exposure. While it is outside the scope of this article to provide an extensive review of research linking stressful events to all diseases, in this section, we consider evidence for the relationships between stressor exposure and a selection of common illnesses responsible for a large proportion of morbidities, disabilities, and deaths worldwide: depression, cardiovascular disease (CVD), infectious diseases, and cancer (see also Cohen et al. 2007).

Depression.—Major stressful life events prospectively predict the premorbid symptoms of depression, anxiety, and fear that are risks for depression (Gotlib & Joormann 2010, Hammen 2016, Turner et al. 1995). They also predict both the clinical onset and subsequent reoccurrences of major depressive disorder (Hammen 2005, Monroe et al. 2009). Individuals who develop depression are estimated to be between 2.5 and 9.4 times as likely to have experienced a major stressful life event prior to the first onset of depression, making recent stressor exposure one of the strongest proximal risk factors for depression in community samples (Kendler et al. 2000, Monroe et al. 2009, Slavich & Irwin 2014). Furthermore, among individuals who are depressed, stressful life events are associated with higher symptom severity, longer duration of illness, and increased likelihood of relapse (Monroe et al. 2009).

Cardiovascular diseases.—Numerous mechanistic studies have documented that exposure to stressful life experiences is associated with the development of premorbid processes and states well recognized as risk factors for clinical CVD onset and progression (Steptoe & Kivimaki 2013). These factors include increased central adiposity, dysregulation of lipid and glucose levels, heightened exposure to inflammation, and elevated resting blood pressure. In line with these mechanistic studies, prospective studies have repeatedly documented that chronic stressful experiences are associated with increased risk for the development of clinical CVD (Dimsdale 2008). Moreover, experiencing chronic stressors predicts both faster progression of CVD and increased mortality from CVD (Steptoe & Kivimaki 2012). Even acute stressors can trigger adverse cardiac events, such as myocardial ischemia, cardiac arrhythmias, cardiomyopathy, and myocardial infarction, among patients with preexisting heart disease (Steptoe & Kivimaki 2013).

Infectious diseases.—Infectious diseases are caused by pathogens such as viruses and bacteria. However, experiencing stressful life events, especially chronic enduring events, can increase an individual's risk of developing illness in response to exposure to an infectious agent (for a review, see Pedersen et al. 2010). Some of the most compelling evidence for the role of stressful events in increasing individuals' risk for developing illness following exposure to a pathogen comes from a series of viral challenge studies conducted by Cohen and colleagues (for an overview, see Cohen 2016). In these studies, healthy adults were experimentally exposed to a virus that causes the common cold and then quarantined and followed for 5–6 days to determine who developed a clinical illness, as manifested by infection (shedding virus) and objective signs of disease (mucus production and congestion). Within this paradigm, exposure to recent and chronic stressful life events has repeatedly been shown to increase an individual's risk of developing clinical illness following inoculation with the challenge virus. While a cold is not generally a serious illness, these findings demonstrate that host resistance to infectious agents can be reduced by stressful events. In the case of a far more serious infectious disease, naturalistic studies of HIV/AIDS conducted since the advent of highly active antiretroviral therapy have found that stressful life events, especially exposure to traumatic experiences, are associated with poorer disease outcomes, including increased viral load, higher risk of developing an opportunistic secondary infection, and increased AIDS-related mortality (Leserman 2008).

Cancer.—Findings regarding whether stressful life events increase cancer risk or progression are much more equivocal than findings for the other conditions discussed above. Mechanistic laboratory studies have demonstrated a role of stressful experiences in modulating physiological processes related to cancer development (for reviews, see Antoni et al. 2006, Fagundes et al. 2017). Conversely, prospective studies of the association between stressful events and cancer onset and progression have not consistently found evidence for stressor exposure as a risk factor (for a review, see Cohen et al. 2007). However, this lack of consistent findings may be due to difficulties in conducting methodologically rigorous, well-powered cancer studies. Consistent with this notion, using meta-analytic techniques, Chida et al. (2008) found that, among studies that they coded as being high in quality, stressful life events were associated with poorer survival among samples of patients with cancer, as well as with higher mortality rates due to cancer in population samples. That being said, cancer is

a heterogeneous disease, and the findings reviewed by Chida et al. were limited to only a relatively narrow set of possible cancer sites. Furthermore, the reported pooled effect sizes were modest, and the authors found evidence for significant publication bias. As such, the true nature of the association between stressor exposure and cancer remains much less clear than for the other diseases discussed above.

Theory versus data.—While exposure to stressful events could theoretically impact any disease that is modulated by associated behaviors or physiology, the evidence concerning stressful events and cancer highlights a divide between what theory suggests and what data show. Health behaviors, hormones, and central nervous system activity are all known to modulate various cancers (Anderson et al. 1994, Antoni et al. 2006, Lutgendorf & Andersen 2015, Sklar & Anisman 1981). However, the strongest conclusion derived from decades of research on stressors and cancer is that stressful events may be associated with decreased cancer survival but are probably not associated with disease incidence (Chida et al. 2008). From a public health perspective, the evidence that exposure to stressful events is associated with cancer survival is interesting and important. However, it is conceptually unclear why the incidence of a disease influenced by the same pathways that are activated by exposure to stressors would not show more empirical associations with stressful experiences (but see Sklar & Anisman 1981). It is possible that this issue may simply reflect eventually surmountable methodological limitations related to studying cancer in humans (Cohen et al. 2007). Nonetheless, one area that may benefit from further development is a better accounting of what disease processes may be less subject to modulation by stressor exposure and why this might be the case.

Fact 3: Most People Exposed to Stressful Events (Even Traumatic Events) Do Not Get Sick

Despite compelling evidence that stressful events have the capacity to impair health, on the whole, most people who experience stressful events do not get sick. This is true both in the case of normative stressful events (i.e., events that happen to most of us sometime in our lifetime, such as a job loss or the loss of an important relationship) and for less common traumatic events (e.g., direct exposure to violence or abuse).

This phenomenon has been highlighted in work exposing otherwise healthy participants to a common cold virus (Cohen et al. 1998). Stressful events were assessed in a sample of 276 participants using the LEDS semistructured interview discussed above (Brown & Harris 1989). Participants were then inoculated with rhinovirus, quarantined, and tracked for the development of a biologically verified cold. As predicted, those reporting an enduring (1 month or more) stressful life event had an increased likelihood of developing a cold compared to those who did not report a stressful life event. Only 72 of 201 participants (35.8%) without a stressful event developed a cold compared to 37 of 75 participants (49.3%) who reported a stressful event. What is often neglected when interpreting these data is that 38 of the 75 participants who reported a stressful life event (50.7%) did not develop a clinical cold.

While exposures to stressful and even traumatic events may not always result in physical illness, one would think that the occurrence of negative mental health outcomes, such as

depression, would be commonplace. Interestingly, this does not appear to be the case. Although stressful life events are consistently found to be related to increased risk for depression, depression is not inevitable. Indeed, Bonanno et al. (2011) have demonstrated across various traumatic events that the majority of exposed individuals are resilient to later psychopathology. For example, in response to a loss of a spouse in later life, 13.2% of adults in the sample experienced the onset of depression following the loss, which is in stark contrast to the 68.2% who showed little to no evidence of depression over a 6-year follow-up period (Maccallum et al. 2015). The remaining percentage of the sample was made up of individuals who were depressed prior to the loss and remained depressed across the sampling frame (7.4%) and those who showed high levels of depression prior to the loss of their spouse that improved following the loss (11.2%). While the percentage of individuals who fall into these different groups vary by stressor exposure (e.g., combat exposure, medical illness, loss of a child) and by psychopathology outcome (e.g., depression, post-traumatic stress disorder), a large segment of those exposed to stressors (35–65%) do not suffer significant mental health problems as a consequence (Bonanno et al. 2011).

Why are some people resilient to stressful events? Accumulating data suggest that several individual difference measures play protective roles. In this regard, reports of greater perceived control, greater self-efficacy, and lesser negative affectivity and rumination have all been associated with psychological resilience in the face of stressful life events (reviewed in Adler & Matthews 1994, Bonanno et al. 2011). Access to social resources has also been shown to promote resilience under stressful circumstances (Cohen 2004). These resources include emotional, instrumental, and informational support. The influence of social support in buffering the negative effects of stressful events goes beyond mental health. For example, a prospective study of over 700 men followed over 7 years found that the presence of stressful events predicted increased risk of mortality only among participants reporting low emotional support. Those with high levels of emotional support were protected (Rosengren et al. 1993).

Fact 4: Stressful Events Do Not Fall Randomly from the Sky

With some limited exceptions (e.g., natural disasters, accidental deaths of friends or family members), stressful event exposures do not occur at random but instead are influenced by both individual differences in environmental circumstances and psychological characteristics. An example of a salient environmental circumstance at play here is the socioeconomic status (SES) of one’s neighborhood. Compared to high-SES neighborhoods, low-SES environments are marked by more frequent and severe stressor exposures, such as overcrowding and the observation and experience of violence (Evans & Kim 2010). Individual SES can similarly influence exposure to stressful events. For example, those with lower SES are more likely to experience a divorce, death of a child, and violent assault than those with higher SES (Adler et al. 1994, Lantz et al. 2005).

Personality factors may also be hidden causes of stressor exposure. For example, divorce is more common in those whose personality is characterized by greater neuroticism or lesser conscientiousness and agreeableness (Roberts et al. 2007). In addition, some cognitive styles, such as a tendency to attribute negative events to stable, global, and internal causes,

can lead individuals to experience more stressful life events. Examined primarily in the context of depression (Hammen 2006), individuals characterized by negative attributional style have been found to generate more interpersonal conflicts, leading to a greater likelihood of experiencing stressful life events, such as the loss of a close relationship (Liu & Alloy 2010). Notably, negative attachment styles, such as anxious attachment, and maladaptive coping strategies, such as avoidant coping, have also been linked to a tendency to experience more future major stressful life events (Barker 2007, Hankin et al. 2005).

Interestingly, individual stressful events themselves may trigger sequences of other events (Cohen et al. 1982, Monroe 1982). Like dominos, when one event occurs, this sets into motion a cascade of subsequent stressors that can result in a clustering of stressor exposures. An example of this could be the loss of a job. An event like this can reverberate through an individual's life, leading to exposure to multiple additional stressors, including residential relocation and increased strain in one's relationships, possibly leading to marital divorce. Divorce could lead to the loss of income, health insurance, and contacts with friends. Moreover, a single stressor can have transgenerational effects. For example, parental job loss can create stressors for children, including a need to change schools (due to relocation of their home), loss of close contacts, and possible parental separation.

Fact 5: Stressful Events May Not Cause Disease in Healthy People

As noted above, there is consistent evidence that exposure to stressful life events predicts increases in risk for disease, particularly in the case of chronic medical conditions such as CVD, asthma, and depression (Monroe et al. 2009, Steptoe & Kivimaki 2013, Wright et al. 1998). However, it is important to emphasize that stressful event exposure may not be the proximate cause of disease. That is, stressful events may not trigger the initial pathogenesis of disease in otherwise healthy people. Rather, events may influence risk for disease by either suppressing the body's ability to fight invading pathogens or exacerbating the progression of ongoing premorbid processes, resulting in the eventual onset of clinically defined disease.

We view the evidence for associations between stressful events and the onset of chronic diseases as equivocal because of the difficulty of identifying when these diseases begin. That is, in many cases, baseline (prior to the onset of the stressful event) measures of disease do not convincingly rule out the possibility of unidentified signs of illness. In turn, studies of the incidence of such diseases may actually be studies of the role of stressful events in the progression of disease, or, in some cases, may reflect preexisting disease resulting in stressor exposure. For example, coronary artery disease (CAD) is marked by the accumulation of plaques in the coronary arteries that, over time, lead to blockage and reduction in blood flow. When it is severe, a reduction in blood flow can result in cardiovascular events such as a heart attack. Although CAD was once thought to be a disease that emerged in midlife, recent research suggests that the premorbid pathogenesis of CAD can begin during the first 2 decades of life (Thurston & Matthews 2009). Thus, what appears to be stressor-triggered disease onset in midlife and older adults may actually be stressor-triggered progression of previously unidentified disease. Identifying premorbid markers of cancer at baseline

involves a similar challenge, with early and premorbid disease often being difficult or impossible to detect (Cohen et al. 2007).

Exposure to stressful events can, however, exacerbate early or premorbid disease states by tipping the balance of an already vulnerable system. For example, heart attacks are a marker of the progression of CAD and occur in persons with underlying atherosclerosis. A study of the 1981 earthquake in Athens, Greece found an increased rate of fatal heart attacks on the days immediately following the earthquake compared to the days that preceded it (Trichopoulos et al. 1983). Similarly, activity from implantable cardioverter defibrillators (devices used on heart disease patients to detect and correct heart rhythm issues) was significantly higher in the 30 days following the September 11 World Trade Center attacks than in the 30 days before (Steinberg et al. 2004). Importantly, these examples suggest that stressful events may contribute to morbidity by triggering cardiovascular events in individuals already burdened by CVD. This association also plays a role in asthma exacerbation. For example, Sandberg et al. (2000) demonstrated that, in children with chronic asthma, the occurrence of severe stressful events, such as the death of a family member or parental divorce, prospectively predicted an asthma exacerbation between 2 and 4 weeks after the event.

The assertion that stressful events may not be the proximal cause of the onset of chronic diseases derives from historical limitations in measuring premorbid and early stage disease in epidemiological studies. It is not a criticism of the wealth of evidence that stressful events can perturb key biological processes that potentially play a role in disease pathogenesis (e.g., inflammatory processes, metabolic dysregulation). In other words, we are not denying the possibility that progressive biological wear and tear that occurs with chronic or cumulative stressful life events may result in increased disease risk (Juster et al. 2010, McEwen 1998). Rather, we are suggesting that the evidence that stressful life events play a causal role in the onset of chronic diseases in otherwise healthy individuals (i.e., without existing disease) is not well supported empirically.

Fact 6: Certain Types of Stressful Events Are Particularly Potent

Not all domains of stressful life events are equally impactful when it comes to shaping an individual's health. Experiences that threaten an individual's sense of competence or status within domains that makeup the individual's core identity appear to be the most costly (Cohen et al. 2016; see also Crocker & Park 2004). Events of this nature generally fall into three broad categories, although there is overlap among categories. These categories are interpersonal problems, loss of social status, and employment difficulties (in particular, un- or underemployment).

Events involving interpersonal problems can be broadly construed as threatening or harmful events that are centered around interactions or relationships with other people. Examples of interpersonal events include ongoing conflict with a spouse, friend, or coworker; a close friend moving away; and the death of a loved one. Stressful events involving other people occur less frequently than positive experiences with others; however, when negative events do occur, they tend to have a more dramatic impact on well-being and health than do positive interpersonal experiences (Rook 1998). Indeed, evidence has accumulated linking

stressful interpersonal events to a variety of negative health outcomes, including heightened risk of depression, upper respiratory infection, hypertension, heart disease, physical disability, and premature mortality (Cohen et al. 1998, Kendler et al. 2003, Rook 2014, Sneed & Cohen 2014).

Interpersonal stressful life events may be problematic for health; however, it is also the case that not all events within this domain are equally potent. Mounting evidence suggests that interpersonal events that specifically threaten an individual's social status (i.e., that are high in social-evaluative threat) may be particularly noxious (Dickerson & Kemeny 2004). Examples of such events include being broken up with by a romantic partner and being intentionally excluded from social activities by one's peers. Studies have shown links between stressful events marked by loss of social status and adverse health outcomes. For example, in a large epidemiological survey, Kendler et al. (2003) found that interpersonal loss was associated with increased risk for developing depression. However, the extent to which depression risk increased depended on the nature of the loss. Individuals who had experienced the death of a loved one were at similarly elevated risk for depression as individuals who broke off the relationship with their romantic partner, whereas individuals who had been broken up with by a romantic partner showed the greatest depression risk. Relatedly, in a multiwave study of youth diagnosed with asthma, Murphy et al. (2015) found that, at study waves when individuals reported having recently experienced social rejection, they showed decreased anti-inflammatory gene signaling and increased asthma symptoms compared to study waves when no rejection had occurred. Importantly, no such associations were found for other types of stressful life events (i.e., interpersonal events without rejection and noninterpersonal events) with similar severity ratings. Results from these studies also converge with research in nonhuman primates that documents threats to social status as a particularly pathogenic type of stressful event (e.g., Cohen et al. 1997, Manuck et al. 1995, Shively & Clarkson 1994).

Employment difficulties, especially becoming unemployed or being underemployed, have adverse implications for role identity, social status, and financial security and are also associated with deleterious health outcomes. For example, in a study that directly compared how various different types of major stressful life events influence disease risk, Cohen et al. (1998) found that un- or underemployment life events lasting at least 1 month, as measured using the LEDS, were the strongest predictors of developing illness among participants experimentally exposed to a cold-causing virus (interpersonal events were the next-strongest predictors of illness). More broadly, epidemiological studies have found that becoming unemployed or underemployed increases risk for depression, CVD, and premature mortality (e.g., Dooley et al. 2000, Gallo et al. 2004, Morris et al. 1994).

Fact 7: Chronic Stressful Events Are Worse than Acute Ones, Except When They Are Not

It is generally thought that stressful life events that last a long time are more harmful than acute ones. This is because, as exposure persists, there are increased probabilities of the stressor being present at points of vulnerability in the disease process; of long-term or permanent changes in the emotional, physiological, and behavioral responses that have

downstream influences on disease (Cohen et al. 2007); and of increased wear and tear on the body (e.g., allostatic load) (McEwen 2004).

However, there are dimensions of chronic events, other than duration per se, that can be important for understanding the health risks that these events pose. Chronic events include both persistent chronic stressors, such as permanent disabilities, parental discord, or chronic job stress, which persist continuously for a long time, and chronic intermittent stressors, such as conflict-filled visits to in-laws or sexual difficulties, which may occur once a day, once a week, or once a month (Cohen et al. 1982). Another type of chronic exposure involves stressor sequences, or series of events that occur over an extended period of time as the result of an initiating event such as job loss, divorce, or bereavement (Cohen et al. 1982, Monroe 1982).

When do chronic events matter?—We propose that chronic events should be associated with a greater risk of facilitating disease processes than should acute events. This belief is in contrast to the adaptation hypothesis—that one adapts to stressors over time, and thus shows fewer effects with increased duration of exposure. The adaptation hypothesis is based primarily on laboratory studies where physiological responses to stressful experiences habituate rather quickly (e.g., Glass & Singer 1972), as well as on work looking at long-term adaptation to physical disability (Schulz & Decker 1985). What are the characteristics of chronic events that result in increased risk versus attenuation over time? One possibility is that continued effects of exposure to prolonged stressful experiences are more likely to occur when events are severely threatening, and habituation or adaptation is more likely to occur when they are less so. Another possibility is that the type of periodicity of the event matters, with random intermittent events inhibiting habituation and continuous or predictable intermittent events promoting adaptation (Glass & Singer 1972). A final possibility is that the underlying biological process is key. Many stressor-elicited changes, for example in immune function (Anderson et al. 1994) and sympathetic activation (Kaplan et al. 1987, Skantze et al. 1998), may persist with the chronicity of a natural stressor; yet others, such as cortisol concentrations (Ockenfels et al. 1995), may habituate over time.

When do acute events matter?—As alluded to above, although it plays less of a role in disease onset, exposure to acute (time-limited) stressful life events, such as taking an important exam, awaiting surgery, or being held up at gunpoint, are thought to play a significant role in exacerbating preexisting disease. For example, among individuals with CAD (atherosclerosis), exposure to acute life stressors is associated with a number of deleterious cardiovascular outcomes such as reduced oxygen delivery to the heart, which, when extreme, results in the death of heart tissue—a heart attack or myocardial infarction (Rozanski et al. 1999). Similarly, among those with asthma (underlying inflammation of the airways), acute events can trigger asthma attacks (Wright et al. 1998).

Others (Baum et al. 1993) have emphasized that traumatic events like rape or physical assault may last a short time but still have long-term effects on risk for disease. They suggest that the impact of a stressful event should be determined not only by the duration of the event, but also by the durations of the ensuing appraisal process, the affective response to the event, and the stress-related physical effects.

Fact 8: Multiple Events May Be More Potent than Individual Ones, or They May Not

Above, we mention that both definitions of stressful life events that focus on adaptation and those that focus on threat suggest the possibility that the risk associated with stressful life events is cumulative. Unexpectedly, research with stressful life event checklists that merely count the number of events that occurred during the previous year results in as good predictions of health outcomes as summing change or threat weights assigned to the events by judges (Turner & Wheaton 1995). Thus, it is true that the more events occur, the greater is the risk, but at the same time, the data do not provide direct evidence that this effect is due to the amount of change or threat that is accumulating.

In contrast, as noted above, research using the LEDS interview suggests that experiencing a single event that meets a moderate or severe threat criterion is sufficient to put people at risk, but that experiencing multiple events does not further increase that risk (Brown & Harris 1989, Wethington et al. 1995). A possible explanation for the LEDS interview's finding that single events predict health outcomes is that the life event checklists may not be doing a good job of defining the content of events. For example, is a divorce that leads to residential relocation and loss of income one event or three? Similarly, are conflicts at work, being underpaid at work, and being overloaded at work separate events, or do they all represent a single bad work environment? The LEDS takes into account the context in which events occur, probably resulting in single events, as assessed by the LEDS, representing multiple events on a life events checklist. Some recent life events checklists have had success with aggregating events into domains (e.g., financial events, legal events, career events, relationships, safety in the home, and medical issues) and counting the number of domains in which someone is experiencing stressors, rather than the number of events across domains (Lee et al. 2017, Shalowitz et al. 1998). Creating domains may better represent the experience of correlated events.

A related question is whether chronic background stressors, e.g., marital discord or a bad work environment, make one more or less responsive to the occurrence of acute events. The hypothesis that exposure to chronic events results in sensitization has been supported by studies of the impact of acute stressors when there is a background of chronic stress on the symptoms and signs of disease in asthmatic children (e.g., Marin et al. 2009; Sandberg et al. 2000, 2004) and on depression among caregivers for the chronically ill (Kiecolt-Glaser et al. 1988); however, this hypothesis has received only mixed support in studies of biomarker responses to acute laboratory stressors in those suffering chronic background stress (Gump et al. 1999). The variability in results could be attributed to multiple differences between studies, for example, differences in definitions of what constitutes a chronic event, whether the chronic event has been resolved or not, the relationship between the domain of the chronic stressful event and the domain of the acute stressor, and the acute stressor study outcome (most outcomes studied in the laboratory are cardiovascular).

Overall, it is impossible at this point to know whether increases in the number of events increases risk for disease. This is because there is no overall agreement as to what constitutes an event. It is not clear whether an event needs to meet a threshold of threat or adaptation, whether events that cluster together (e.g., divorce and moving) should be considered a single experience or multiple ones, or whether event domains are a better way

of defining the stress experiences than the occurrence of single events. Studies providing better comparisons of these possibilities would help in providing a clearer answer to this question.

Fact 9: Stressful Events Vary in Frequency and Potency as a Function of Where an Individual Is in the Life Course

There is substantial variability in individuals' day-to-day lives. However, structured around this variability are predictable life events that make up the typical life course. These events are common in the population, routinely happen during a particular life stage, and are consistent with sociocultural norms (Schulz & Rau 1985). Examples of such events include finishing school, getting married, and having a child during the earlier adult years and retirement from the workforce and the death of a spouse during the later adult years. Individuals have expectations about when such events are supposed to happen, and violations of these expectations can have deleterious consequences for health and well-being. To illustrate, consider the death of a spouse. Losing a loved one can represent a stressful event regardless of age (Bonanno & Kaltman 1999). Yet as painful as the death of a spouse might be, such an event is more normative among older adults relative to the same loss experienced earlier in the life course. As a result, losing a spouse should be more strongly associated with negative outcomes when it occurs earlier in life than when it occurs in later decades. Consistent with this formulation, meta-analytic evidence shows that the age at which individuals lose a spouse moderates mortality risk, with the association between stress and mortality being stronger among younger individuals than among older individuals (Shor et al. 2012). Violations of expectations of when normative events should happen also include situations where expected events do not occur; for example, not graduating high school, not getting married, or not being promoted at expected times have the potential to exert similar pathogenic effects as stressful life events that do occur (Schulz & Rau 1985).

In addition to expectations around when particular types of stressful events should or should not happen over the life course, there is evidence that there are sensitive periods of life when stressful events may exact a more pronounced and long-lasting toll on health. Childhood appears to be a particularly important sensitive period, with numerous studies linking adverse childhood experiences to increased risk of developing chronic illnesses later in life, as well as increased mortality risk (e.g., Anda et al. 2009, Norman et al. 2012, Wegman & Stetler 2009). Adverse childhood experiences are generally conceptualized as stressful early life events comprising both ongoing difficulties (e.g., parental abuse or neglect) and acute time-limited exposures with long-term threat implications (e.g., witnessing a violent crime or being sexually assaulted). Experiencing adversity during childhood may set an individual on a trajectory to being exposed to more stressors over the life course, and such excess exposure may subsequently increase disease risk (Pearlin et al. 2005). Furthermore, adverse childhood experiences are also thought to increase risk for negative health outcomes later in life by generating enduring changes in both biological processes and behavioral proclivities (Repetti et al. 2002, Taylor 2010). In some cases, such changes may confer shorter-term adaptive advantages to individuals in the context of the adverse childhood environment. However, these shorter-term advantages may come at a cost with regards to later-life disease risk (Cohen et al. 1986, Danese & McEwen 2012, Miller et al. 2011).

Fact 10: Different Types of Stressful Events Influence Women and Men

Underlying physiological differences between the biological sexes, along with differential evolutionary pressures, play a role in shaping men's and women's physiological and behavioral responses to stressful experiences (Bale & Epperson 2015, Taylor et al. 2000). However, the extent to which men and women differ in the types of stressful events that they are exposed to is thought to be driven more by differences in socialized gender roles than by underlying physiology. As reviewed by Dedovic et al. (2009), in Western cultures, men are historically more likely than women to be encouraged from an early age to develop self-focused agentic goals (e.g., getting a good job). Conversely, women are more likely than men to be encouraged to develop socially interdependent communal goals (e.g., taking care of a family). These differently cultivated goal motivations ultimately shape the sorts of experiences that young men and women seek as they develop into adolescents and adults. As a result, the types of stressful events that men and women experience should theoretically vary as a function of gender socialization.

Consistent with the idea that socialized gender roles predispose men and women to different stressful events, researchers have argued that men are more likely to be exposed to achievement-related stressful experiences such as unemployment, while women are more likely to be exposed to interpersonal stressful experiences such as caregiving (for a review, see Helgeson 2011). Moreover, whereas men tend to only report stressful events that occur directly to them, women are more likely to also report exposure to stressful events that occur to close others (Kessler & McLeod 1984, Turner et al. 1995). However, while this theoretical orientation predicting differential patterning of stressful life experiences as a function of gender continues to permeate the literature, it may not be consistent with available data. In particular, a meta-analysis of 119 studies published between 1960 and 1996 found that women consistently reported greater exposure to stressful events than men across domains, including in both interpersonal and work domains (Davis et al. 1999). It is possible that changing sociocultural norms regarding women in the workplace have closed the gap in work-related stressor exposure, as women place more importance on employment and financial success now than they did in the past (e.g., McLeod et al. 2016).

There are fewer studies addressing the extent to which gender differences in exposure to stressful life events are associated with differential vulnerability to illnesses. The clearest evidence for differential vulnerability comes from studies examining sex disparities in depression risk (Hammen 2005). While depression risk is similar between males and females during childhood, starting during adolescence, females' risk for depression increases relative to males, a pattern that remains consistent well into adulthood (Cyranowski et al. 2000). This finding is thought to be due at least in part to women developing more sensitivity to what is happening within their social networks and thus being exposed to more interpersonal stressful life events than men (Helgeson 2011, Kessler & McLeod 1984). Importantly, exposure to interpersonal events tends to be more strongly associated with depression onset for women than for men (Hammen 2005). Interestingly, women's heightened vulnerability to depression following stressful events may also help explain why, compared to men, women tend to experience worse clinical outcomes due to

morbidities modulated by depression, such as CVD and metabolic diseases (for reviews, see Low et al. 2010; Moller-Leimkühler 2008, 2010; Murphy & Loria 2017).

REFLECTIONS AND CONCLUSIONS

What We Know About Stressful Life Events and Disease Risk

What we can be sure of is that stressful life events predict increases in severity and progression of multiple diseases, including depression, cardiovascular diseases, HIV/AIDS, asthma, and autoimmune diseases. Although there is also evidence for stressful events predicting disease onset, challenges in obtaining sensitive assessments of premorbid states at baseline (for example, in cancer and heart disease) make interpretation of much of these data as evidence for onset less compelling.

In general, stressful life events are thought to influence disease risk through their effects on affect, behavior, and physiology. These effects include affective dysregulation such as increases in anxiety, fear, and depression. Additionally, behavioral changes occurring as adaptations or coping responses to stressors, such as increased smoking, decreased exercise and sleep, poorer diets, and poorer adherence to medical regimens, provide important pathways through which stressors can influence disease risk. Two endocrine response systems, the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenal-medullary (SAM) system, are particularly reactive to psychological stress and are also thought to play a major role in linking stressor exposure to disease. Prolonged or repeated activation of the HPA axis and SAM system can interfere with their control of other physiological systems (e.g., cardiovascular, metabolic, immune), resulting in increased risk for physical and psychiatric disorders (Cohen et al. 1995b, McEwen 1998).

Chronic stressor exposure is considered to be the most toxic form of stressor exposure because chronic events are the most likely to result in long-term or permanent changes in the emotional, physiological, and behavioral responses that influence susceptibility to and course of disease. These exposures include those to stressful events that persist over an extended duration (e.g., caring for a spouse with dementia) and to brief focal events that continue to be experienced as overwhelming long after they have ended (e.g., experiencing a sexual assault). Even so, acute stressors seem to play a special role in triggering disease events among those with underlying pathology (whether premorbid or morbid), such as asthma and heart attacks.

One of the most provocative aspects of the evidence linking stressful events to disease is the broad range of diseases that are presumed to be affected. As discussed above, the range of effects may be attributable to the fact that many behavioral and physiological responses to stressors are risk factors for a wide range of diseases. The more of these responses to stressful events are associated with risk for a specific disease, the greater is the chance that stressful events will increase the risk for the onset and progression of that disease. For example, risk factors for CVD include many of the behavioral effects of stressors (poor diet, smoking, inadequate physical activity). In addition, stressor effects on CVD (Kaplan et al. 1987, Skantze et al. 1998) and HIV (Capitanio et al. 1998, Cole et al. 2003) are mediated by

physiological effects of stressors (e.g., sympathetic activation, glucocorticoid regulation, and inflammation).

It is unlikely that all diseases are modulated by stressful life event exposure. Rare conditions, such as those that are genetic and of high penetrance, leave little room for stressful life events to play a role in disease onset. For example, Tay-Sachs disease is an autosomal recessive disorder expressed in infancy that results in destruction of neurons in both the spinal cord and brain. This disease is fully penetrant, meaning that, if an individual carries two copies of the mutation in the *HEXA* gene, then they will be affected. Other inherited disorders, such as Huntington's disease, show high penetrance but are not fully penetrant, leaving room for environmental exposures, behavioral processes, and interactions among these factors to influence disease onset. Note that, upon disease onset, it is unlikely that any disease is immune to the impact of stressor exposure if pathways elicited by the stressor are implicated in the pathogenesis or symptom course of the disease.

What We Do Not Know About Stressful Life Events and Disease Risk

There are still a number of key issues in understanding how stressful events might alter disease pathogenesis where the data are still insufficient to provide clear answers. These include the lack of a clear conceptual definition of what constitutes a stressful event. Alternative approaches (adaptation, threat, goal interruption, demand versus control) overlap in their predictions, providing little leverage for empirically establishing the unique nature of major stressful events. The lack of understanding of the primary nature of stressful events also obscures the reasons for certain events (e.g., interpersonal, economic) being more potent.

Two other important questions for which we lack consistent evidence are whether the stress load accumulates with each additional stressor and whether previous or ongoing chronic stressors moderate responses to current ones. The nature of the cumulative effects of stressors is key to obtaining sensitive assessments of the effects of stressful events on disease and for planning environmental (stressor-reduction) interventions to reduce the impact of events on our health.

Evidence that single events may be sufficient to trigger risk for disease has raised two important questions. First, are some types of events more potent than others? We address this question above (in the section titled Fact 6: Certain Types of Stressful Events Are Particularly Potent) using the existing evidence, but it is important to emphasize the relative lack of studies comparing the impact of different stressors on the same outcomes (for some exceptions, see Cohen et al. 1998, Kendler et al. 2003, Murphy et al. 2015). Second, are specific types of events linked to specific diseases? This question derives from scattered evidence of stressors that are potent predictors of specific diseases [e.g., social loss for depression (Kendler et al. 2003), work stress for CHD (Kivimäki et al. 2006)] and of specific stress biomarkers [e.g., threats to social status leading to cortisol responses (Denson et al. 2009, Dickerson & Kemeny 2004)]. While it is provocative, there are no direct tests of the stressor-disease specificity hypothesis. A proper examination of this theory would require studies that not only conduct broad assessments of different types of stressful life events, but also measure multiple unique diseases to draw comparisons. Such studies may not be

feasible due to the high costs of properly assessing multiple disease outcomes and the need for large numbers of participants to obtain sufficient numbers of persons developing (incidence) or initially having each disease so as to measure progression. Comparisons of limited numbers of diseases proposed to have different predictors (e.g., cancer and heart disease) are more efficient and may be a good initial approach to this issue.

Another area of weakness is the lack of understanding of the types of stressful events that are most salient at different points in development. For example, although traumatic events are the type of events studied most often in children, the relative lack of focus on more normative events leaves us with an incomplete understanding of how different events influence the current and later health of young people. Overall, the relative lack of comparisons of the impact of the same events (or equivalents) across the life course further muddies our understanding of event salience as we age.

It is noteworthy that the newest generation of instruments designed to assess major stressful life events has the potential to provide some of the fine-grained information required to address many of the issues raised in this review (for a review, see Anderson et al. 2010; see also Epel et al. 2018). For example, the Life Events Assessment Profile (LEAP) (Anderson et al. 2010) is a computer-assisted, interviewer-administered measure designed to mimic the LEDS. Like the LEDS, the LEAP assesses events occurring within the past 6–12 months, uses probing questions to better define events, assesses exposure duration, and assigns objective levels of contextual threat based on LEDS dictionaries. Another instrument, the Stress and Adversity Inventory (STRAIN) (Slavich & Shields 2018), is a participant-completed computer assessment of lifetime cumulative exposure to stressors. The STRAIN assesses a range of event domains and timing of events (e.g., early life, distant, recent) and uses probing follow-up questions. Both the LEAP and the STRAIN are less expensive and time consuming than the LEDS and other interview techniques and are thus more amenable to use in large-scale studies.

The fundamental question of whether stressful events cause disease can only be rigorously evaluated by experimental studies. Ethical considerations prohibit conducting experimental studies in humans of the effects of enduring stressful events on the pathogenesis of serious disease. A major limitation of the correlational studies is insufficient evidence of (and control for) selection in who gets exposed to events, resulting in the possibility that selection factors such as environments, personalities, or genetics are the real causal agents. The concern is that the social and psychological characteristics that shape what types of stressful events people are exposed to may be directly responsible for modulating disease risk. Because it is not possible to randomly assign people to stressful life events, being able to infer that exposure to stressful events causally modulates disease will require the inclusion of covariates representing obvious individual and environmental confounders, as well as controls for stressor dependency—the extent to which individuals are responsible for generating the stressful events that they report.

Even with these methodological limitations, there is evidence from natural experiments that capitalize on real-life stressors occurring outside of a person’s control, such as natural disasters, economic downsizing, or bereavement (Cohen et al. 2007). There have also been

attempts to reduce progression and recurrence of disease using experimental studies of psychosocial interventions. However, clinical trials in this area tend to be small, methodologically weak, and not specifically focused on determining whether stress reduction accounts for intervention-induced reduction in disease risk. Moreover, trials that do assess stress reduction as a mediator generally focus on the reduction of nonspecific perceptions of stress and negative affect instead of on the elimination or reduction of the stressful event itself. In contrast, evidence from prospective cohort studies and natural experiments is informative. These studies typically control for a set of accepted potentially confounding demographic and environmental factors such as age, sex, race or ethnicity, and SES. It is also informative that the results of these studies are consistent with those of laboratory experiments showing that stress modifies disease-relevant biological processes in humans and with those of animal studies that investigate stressors as causative factors in disease onset and progression (Cohen et al. 2007).

Despite many years of investigation, our understanding of resilience to stressful life events is incomplete and even seemingly contradictory (e.g., Brody et al. 2013). Resilience generally refers to the ability of an individual to maintain healthy psychological and physical functioning in the face of exposure to adverse experiences (Bonanno 2004). This definition suggests that when a healthy individual is exposed to a stressful event but does not get sick and continues to be able to function relatively normally, this person has shown resilience. What is less clear is whether there are certain types of stressful events for which people tend to show greater resilience than for others. It seems likely that factors that increase stressor severity, such as imminence of harm, uncontrollability, and unpredictability, also decrease an event's potential to be met with resilience. Additionally, it may be possible that stressful events that are more commonly experienced are easier to adapt to due to shared cultural experiences that provide individuals with expectations for how to manage events. Conversely, less common events (e.g., combat exposure) or experiences that carry significant sociocultural stigma (e.g., rape) might be less likely to elicit resilience. As efforts to test interventions to promote resilience continue to be carried out, careful characterizations of stress exposures, including the complexities discussed in this review, will be critical to understanding the heterogeneity in physical and mental health outcomes associated with stressful life events.

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