Social Science & Medicine 73 (2011) 615–622

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Sex, stressful life events, and adult onset depression and alcohol dependence: Are men and women equally vulnerable?

Natalie Slopen [a,b,*], David R. Williams [a,c], Garrett M. Fitzmaurice [d], Stephen E. Gilman [a,e]

[a] Department of Society, Human Development, and Health, Harvard School of Public Health, USA
[b] Center on the Developing Child, Harvard University, USA
[c] Department of African and African American Studies, Harvard University, USA
[d] Department of Biostatistics, Harvard School of Public Health, USA
[e] Department of Epidemiology, Harvard School of Public Health, USA

ARTICLE INFO

Article history:
Available online 6 July 2011

Keywords:
Stressful life events
Major depression
Alcohol dependence
Sex
Stress diathesis
United States
National epidemiologic survey on alcohol and related conditions (NESARC)

ABSTRACT

Higher rates of major depression (MD) among females, and of alcohol dependence (AD) among males, are among the most routinely reported findings in psychiatric epidemiology. One of the most often pursued explanations for sex differences in both disorders suggests that males and females have a differential vulnerability to stressors, which is manifested in sex-specific ways (MD for females, AD for males). However, existing evidence in support of this explanation is mixed. In the present study, we investigated sex differences in the association between stressful life events and MD and AD in a large national sample of adults in the United States ($n = 32{,}744$) using a prospective design. Logistic regression was used to estimate associations between stressful life events and both MD and AD; sex-specific effects of stress on MD and AD were evaluated by testing interaction terms between sex and stressors in the prediction of both outcomes. The number of stressful life events was predictive of first onset MD and AD. This was true for both males and females, and sex-by-stress interaction terms did not support the hypothesis that sex-specific responses to stressful life events lead to sex differences in first onset of MD and AD among adults. These results indicate the resistance of sex differences in MD and AD to simple explanations, and suggest the need for more nuanced models that incorporate both physiological and social aspects of vulnerability.

Introduction

Major depression (MD) is approximately twice as common in females compared to males (Kessler, 2003), whereas alcohol dependence (AD) is approximately twice as common in males compared to females (Hasin, Stinson, Ogburn, & Grant, 2007). Both MD and AD present an enormous burden to individuals and society: the World Health Organization estimates that depression is the leading cause of years lost to disability for both females and males, and alcohol use disorders are the second leading cause of years lost to disability for males (World Health Organization, 2008). Researchers have attempted to determine the origin of sex differences in MD (Hyde, Mezulis, & Abramson, 2008; Piccinelli & Wilkinson, 2000) and AD (Hensing & Spak, 2009; Wilsnack, Wilsnack, Kristjanson, Vogeltanz-Holm, & Gmel, 2009), yet many questions remain unanswered (Holmila & Raitasalo, 2005; Piccinelli & Wilkinson, 2000).

Stressful life events are associated with an increased risk of both MD (Kessler, 1997) and AD (Dawson, Grant, & Ruan, 2005; Lloyd & Turner, 2008); the current study investigates whether sex-specific responses to stressors explain sex differences in both disorders. It has long been hypothesized that females are more likely to report internalizing symptoms in response to stress (e.g., somatization, affective or anxiety disorders), while males are more likely to report externalizing symptoms in response to stress (e.g., aggression or substance abuse disorders) (Aneshensel, Rutter, & Lachenbruch, 1991; Conger, Lorenz, Elder, Simons, & Ge, 1993). If such differential vulnerability exists, it would explain the observed sex differences in MD and AD.

Theoretically, sex differences in disorders would be predicted by stress–diathesis models of psychopathology, wherein one sex or the other has a pre-existing vulnerability (i.e., diathesis) to develop the disorder once exposed to a stressor (Ingram & Luxton, 2005). According to stress–diathesis theory, stressful events present

* Corresponding author. Center on the Developing Child, Harvard University, 50 Church Street, 4th Floor, Cambridge, MA 02139, USA. Tel.: +1 617 733 0309.
E-mail address: nslopen@hsph.harvard.edu (N. Slopen).

0277-9536/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.socscimed.2011.06.022

a challenge to the adaptive capacity of the individual, and stable characteristic(s) of the individual (i.e., diathesis factors) will influence subsequent vulnerability to disorders (Bleuler, 1963; Meehl, 1962). Observing sex differences in the association between stress and psychopathology, ruling out differential stress exposure, would therefore be consistent with the existence of a sex-specific diathesis. What constitutes the actual diathesis that is responsible for sex differences in psychiatric disorders could include a wide range of factors. For example, genetic or other physiologic (e.g., hormonal) differences between the sexes could contribute to sex differences in the vulnerability to stressors; in addition, cognitive and interpersonal variables could also function as potential vulnerabilities (Monroe & Simons, 1991). Therefore, determining the nature of sex-specific stress responses could provide important insights into the theoretical underpinnings of sex differences in MD and AD, as well as provide insights into sex-specific etiologies of both disorders.

Evidence for and against sex-specific stress responses

There is inconclusive evidence for sex-specific effects of stress in the development of higher rates of MD among females, and higher rates of AD among males (Dawson et al., 2005; Kendler, Thornton, & Prescott, 2001; Maciejewski, Prigerson, & Mazure, 2001; Perreira & Sloan, 2001). Maceijewski and colleagues (Maciejewski et al., 2001) found that among males and females who did not experience a stressful life event there was no sex difference in MD; yet, females who had been exposed to a stressful life event had a threefold increase in risk for MD relative to males exposed to a stressful life event. In contrast, other research has found little support for elevated risk for MD for females following exposure to stress: in a study of adolescents, Turner and Lloyd did not find a sex difference in the likelihood that cumulative stress (i.e., a count of events) was associated with risk for MD (Turner & Lloyd, 2004). Moreover, some studies have even demonstrated a greater impact of certain stressful life events on MD among males (Bruce & Kim, 1992; Kendler et al., 2001). For instance, Kendler and colleagues (Kendler et al., 2001) found that males were more likely than females to become depressed following a divorce/separation and work problems, whereas females were more likely to become depressed following problems of getting along with others. The mixed evidence from these studies suggests that gendered stress reactions that result in MD, if they exist, may not function equally for all types of stressors; however, it is difficult to discern a specific pattern regarding the types of stressors that are more likely to result in MD among males and females.

Similar inconsistencies exist in the literature on sex differences in AD. Some evidence supports a higher risk of AD among males than females following exposure to stressful life events (Dawson et al., 2005; Perreira & Sloan, 2001; San Jose, Van Oers, Van de Mheen, Garretsen, & Mackenbach, 2000). For example, using data from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions, Dawson et al. (2005) found that the association between the number of stressful life events and alcohol consumption was more pronounced among males than females, and also that particular stressful life events (i.e., legal and job-related stressors) differentially impacted the level of alcohol consumption among males. In contrast, however, Lloyd and Turner (2008) found no sex differences in the association between negative life events and AD in a community sample of adolescents. The inconsistent findings for both MD and AD may be due to a number of factors that differed across the studies, including (1) study design (e.g., prospective versus retrospective report; frequency of measurement; duration of follow-up), (2) age of populations sampled (adolescents, adults, older adults), (3) types of stressors and level of detail considered (daily hassles, chronic exposures, acute major life events), and (4) outcome measure (symptoms versus diagnostic outcome, first onset versus recurrent episode).

Methodological requirements for demonstrating sex-specific stress responses

In order to determine whether sex-specific stress responses can account for sex differences in MD and AD, establishing the causal ordering between stress exposure and psychiatric outcome is essential. This is a challenging feat for cross-sectional studies, including those that use retrospective reports for experiences over the life course, yet many prior studies in this area have collected information about exposures and outcomes in the same interview (Dawson et al., 2005; Nazroo, Edwards, & Brown, 1997; Turner & Lloyd, 2004). In cross-sectional research, any observed correlation between stressful life events and psychiatric outcomes could be due instead to (a) differential recall for stressful life events among individuals with disorders, and (b) the effects of disorders on eliciting stressful life events (e.g., the stress-generation hypothesis (Hart & Fazaa, 2004; Rudolph, Flynn, Abaied, Groot, & Thompson, 2009; Shih & Eberhart, 2008)). For example, in a study of stress and alcohol misuse, researchers (Hart & Fazaa, 2004) divided stressful life events into two categories: events that are not likely to be caused by alcohol misuse, and events that could likely be a consequence of alcohol misuse. Events that were judged as being a likely consequence of alcohol misuse were much more strongly related to alcohol misuse; these results are more consistent with a causal effect of disorders on stressors than a causal effect of stressors on disorders.

It is also necessary to account for an individual's prior history of psychiatric disorders (Kessler, 2003), given that a history of disorders is predictive of current stressors as well as future disorder (Kessler & Magee, 1993; O'Doherty, 1991). Finally, stressful life events may be more strongly related to first onset disorders than to recurrent disorders (Post, 1992). As a result, failure to differentiate between the influence of stressors on first versus recurrent episodes impedes our understanding of the role of stress in the etiology of disorders, and consequently in the causes of sex differences in disorders.

The present research investigates whether females are more likely than males to experience a first onset of MD following stressful life events, and whether males are more likely than females to experience a first onset of AD following stressful life events. This study improves on prior research by utilizing a large, nationally-representative sample of the United States population with 2 waves of data collection, assessing stressful life events prior to the assessment of first onset disorders, and defining psychiatric outcomes according to diagnostic criteria (American Psychiatric Association, 2000). Our analysis will examine differential reactivity to stressors for males and females, defined in the aggregate as the number of stressful life events in the past 12 months, and also by the occurrence of specific stressful life events.

Methods

Sample

The sample for the current study includes participants in Waves 1 (2001–2002) and 2 (2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationwide representative household survey of adults in the United States (B. F. Grant, Kaplan et al., 2003). At both waves, face-to-face interviews were conducted by trained non-clinician United States Census Bureau Field Representatives using the Alcohol Use Disorder and Associated Disabilities Interview Schedule – DSM-IV Version

(AUDADIS-IV). The NESARC used a multistage stratified design (B. F. Grant, Kaplan et al., 2003) that enrolled 43,093 adults from all 50 states. The sample included military personnel living off base, and individuals living in group quarters such as university dormitories. The NESARC over-sampled young adults aged 18–24, and Non-Hispanic Black and Hispanic housing units. The overall response rate at Wave 1 was 81 percent. Among the 43,093 individuals who participated in Wave 1, 39,959 were eligible to participate in the Wave 2 interview (B. Grant, Kaplan, & Stinson, 2007). Individuals were ineligible if they were deceased ($n = 1403$), on active duty in the armed forces for the duration of the follow-up period ($n = 950$), deported, or experiencing mental or physical impairment ($n = 781$).

Among the eligible 39,595 individuals, 34,653 individuals participated in Wave 2 (86.7%). The sample used in our analysis only included those individuals who had complete information for the variables required for our analysis, and who had no history of MD or AD prior to the baseline interview. A total of 393 individuals (1.13%) were excluded due to missing information, and 1516 were not eligible because they had a prior history of both MD and AD at baseline (4.37%); therefore, 32,744 participants were included in our analyses. The average duration between the Wave 1 and Wave 2 interviews was 36.6 months. Data were weighted to take into account design characteristics, over-sampling, and non-response, and were adjusted to be representative of the United States population according to the 2000 census.

Measures

Stressful life events

Participants were asked about their experiences of 12 different types of stressful life events in the 12-month period prior to the Wave 1 interview; individuals provided a yes/no response for each of the items. The inventory of events collected information pertaining to health stressors, social stressors, job stressors, and legal stressors (full list provided in Table 2). We created a cumulative stress score that is a count of the number of events reported; we grouped individuals who reported 5 or more stressors into a single category due to sparseness of data at high values.

Assessment of major depression and alcohol dependence

MD and AD that first occurred during the 3-year follow-up period, assessed at the Wave 2 interview, were based on DSM-IV criteria for major depressive episode and alcohol dependence (American Psychiatric Association, 2000). The test–retest reliability for the AUDADIS measures of MD and AD were good (B. F. Grant, Dawson et al., 2003). We chose to use first onset of disorder occurring any time after the Wave 1 interview as the outcome because our primary interest was the role of stressful events in the development of first onset disorder, and to ensure that the disorder developed (for the first time) subsequent to the stressful life event reported to occur in the 12 months preceding the Wave 1 interview.

Demographic variables

Several Wave I demographic variables were included as control variables. These were age, race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Non-Hispanic American Indian/Alaskan Native, Non-Hispanic Asian/Native Hawaiian/Pacific Islander, and Hispanic or Latino), marital status (currently married, currently separated/divorced, currently widowed, and never married), education (less then high school, high school degree, some college or associates degree, bachelor's degree, graduate degree), income-to-needs ratio (defined using criteria established by the United States Bureau of the Census), and nativity (i.e., whether or not the individual was born in the United States). We also adjusted for other mood, substance, and anxiety disorders in the 12-months prior to Wave 1, based on prior evidence of comorbidity between psychiatric disorders (B. F. Grant et al., 2009); these disorders were measured using the AUDADIS at Wave 1. In models to predict MD, we included indicator variables for any other mood disorders (dysthymia, mania, and hypomania), substance disorder (any drug or alcohol abuse or dependence; drugs include amphetamines, opioids, sedatives, tranquilizers, cocaine, inhalants/solvents, hallucinogens, cannabis, heroin, and "other" drugs), and anxiety disorder (panic disorder, social and specific phobias, and generalized anxiety disorder). In models to predict AD, we included indicator variables for any other substance disorders (drug dependence and alcohol or drug abuse), mood disorder (major depression, dysthymia, mania, and hypomania), and anxiety disorders.

Table 1
Sociodemographic characteristics of participants in analyses predicting first onset of major depression or first onset of alcohol dependence at Wave 2 of the National Epidemiological Study on Alcohol and Related Conditions ($N = 32744$).

	N	% or mean[a] (SE)
Major depression		
Lifetime diagnosis at Wave 1[b]	5044	14.49 (0.32)
First onset since Wave 1	1780	5.20 (0.17)
Alcohol dependence		
Lifetime diagnosis at Wave 1 [c]	2422	8.35 (0.27)
First onset since Wave 1	940	2.99 (0.13)
Demographic characteristics		
Age (mean)	32744	45.39 (0.18)
Education		
< High school	5458	14.67 (0.48)
High school	9447	29.14 (0.54)
Some college	9800	30.40 (0.41)
Bachelor's degree	5399	17.29 (0.46)
Graduate degree	2640	8.50 (0.32)
Household income (mean)	32744	53757.66 (913.45)
Race/ethnicity		
Non-Hispanic African American	6325	11.22 (0.68)
Native American/American Ind.	523	2.09 (0.18)
Asian	928	4.38 (0.54)
Hispanic/Latino	6078	11.67 (1.21)
Non-Hispanic White	18890	70.63 (1.57)
Marital status		
Married/partnered	17652	63.88 (0.50)
Divorced	5038	9.95 (0.20)
Widowed	2948	6.16 (0.15)
Never married	7106	20.01 (0.48)
Born outside of United States	5192	14.15 (1.40)
Disorders in 12 months prior to Wave 1		
Any mood disorder[d]	2828	8.03 (0.22)
Any alcohol/drug abuse or dependence[e]	2352	7.75 (0.23)
Any anxiety disorder[f]	3543	10.29 (0.31)
# of stressful life events 12 m prior to W1 interview:		
0	10105	30.78 (0.58)
1	8221	25.57 (0.34)
2	7041	21.51 (0.30)
3	3607	11.01 (0.23)
4	1814	5.37 (0.17)
5+	1956	5.77 (0.20)
# of stressful life events (mean)	32744	1.56 (0.02)

[a] Percent is presented, unless stated otherwise in left-hand column.
[b] Excluded from analyses predicting first onset of major depression.
[c] Excluded from analyses predicting first onset of alcohol dependence.
[d] Any mood disorder includes major depression, dysthymia, mania, and hypomania.
[e] Any alcohol/drug abuse or dependence (drugs include amphetamines, opioids, sedatives, tranquilizers, cocaine, inhalants/solvents, hallucinogens, cannabis, heroin, and "other" drugs).
[f] Any anxiety disorders includes primary panic disorder, social and specific phobias, and generalized anxiety disorder.

Analytic strategy

We investigated the sex-specific effects of stress on incident MD and AD separately. In analyses of MD, we excluded all individuals

Table 2
Stressful life events in the 12 months prior to Wave 1 of the National Epidemiological Study on Alcohol and Related Conditions ($N = 32,744$).

Stressful life events reported in 12 m prior to Wave 1 interview:	Prevalence (males and females)		Sex difference in exposure[a] (female−male)	95% confidence interval
	%	(SE)		
Did any of your family members or close friends die?	31.25	(0.36)	3.08	(1.95, 4.20)
Did any of your family members or close friends have a serious illness or injury?	36.25	(0.51)	6.25	(4.98, 7.52)
Did you move or have anyone new come to live with you?	15.36	(0.36)	0.99	(0.04, 2.02)
Were you fired or laid off from a job?	5.97	(0.19)	−2.74	(−3.42, −2.05)
Were you unemployed and looking for a job for more than month?	8.00	(0.23)	−1.34	(−2.08, −0.59)
Have you had trouble with your boss or a coworker?	7.54	(0.21)	0.28	(−0.42, 0.98)
Did you change jobs, job responsibilities or work hours?	21.73	(0.42)	−1.72	(−2.91, −0.53)
Did you get separated or divorced or break off a steady relationship?	4.81	(0.14)	0.79	(0.24, 1.34)
Have you had serious problems with a neighbor, friend, or relative?	4.96	(0.18)	2.23	(1.67, 2.80)
Have you experienced a major financial crisis, declared bankruptcy, or more than once not been able to pay your bills on time?	9.64	(0.26)	1.79	(1.03, 2.55)
Did you or a family member have trouble with the police, get arrested or get sent to jail?	4.84	(0.18)	−0.25	(−0.78, 0.29)
Were you or a family member the victim of any type of crime?	6.13	(0.22)	−0.41	(−1.01, 0.19)

[a] Sex difference in report of stressors were calculated by subtracting male exposure from female exposure. Positive values indicate stressors with a higher prevalence for females, and negative values indicate stressors with a higher prevalence for males.

with a history of depression prior to Wave 1 ($N = 6560$), which resulted in a sample of 27,770 for models of MD. In analyses of AD, we excluded individuals with a lifetime history of AD prior to Wave 1 ($N = 3938$); accordingly, the sample for the AD analyses included 30,322 individuals. We fitted logistic regression models for MD and AD that included sex, the cumulative stress score, and the sex−stress score interaction. Using the regression coefficients from the model that included the sex−stress score interaction, we estimated sex-specific odds ratios for the cumulative stress score. We also fitted sex-stratified models for MD and AD in which we entered the cumulative stress score as a categorical variable (1, 2, 3, 4, or ≥5) in order to investigate possible threshold effects. All models included the demographic controls (age, race/ethnicity, marital status, education, poverty ratio, nativity, and other disorders at baseline). In secondary analyses, we disaggregated the cumulative stress score to examine the effect of each individual event (using 12 separate models), and tested for significant interactions between sex and each of the events. Statistical analyses were performed using SAS-callable SUDAAN 10.0, in order to account for the complex multi-stage sampling design.

Results

The proportion of the sample with first onset MD during the NESARC follow-up period was 4.96% (3.70% among males, 6.09% among females; $p < .0001$). For first onset of AD, the proportion was 2.85% (3.80% among males, 1.98% among females; $p < .0001$). Table 1 presents sample characteristics for individuals included in either the MDD or AD analyses, which represents 95.6% of participants who completed Wave 2 (1516 participants were not eligible for both the MDD and AD analyses because they had a prior history of both disorders at Wave 1). The mean age of the sample was 45.4 years, 63.9% was married, and 14.2% was born outside of the United States.

Prevalence of stressful life events among males and females

Table 2 presents the prevalences of stressful life events in the analytic sample, and the sex difference in the prevalence of each event. Report of a family member or close friend with a serious illness or injury was the only stressful life event where the prevalence between males and females differed by more than 5%. Males and females reported a relatively similar number of events in 12 months prior to Wave 1. The mean number of stressful events was 1.61 (SE = 0.02) for females, and 1.52 (SE = 0.02) for males. Given that males and females reported similar exposure to these stressful life events, it is unlikely that differential exposure to these stressors is a mechanism for the observed sex differences in MD and AD.

Responsivity to cumulative stress

Fig. 1a and b show the unadjusted prevalence of first onset MD and AD between Wave 1 and Wave 2, by number of stressful events, among those at risk for first onset of disorder. For both disorders, the prevalence was positively associated with number of events for both males and females. If the stress−diathesis model was consistent with the gender differences observed for MD and AD, we would expect that the sex-specific lines would be non-parallel and show a steeper slope for females in Fig. 1a, and a steeper slope for males in Fig. 1b. However, Fig. 1a and b do not show patterns

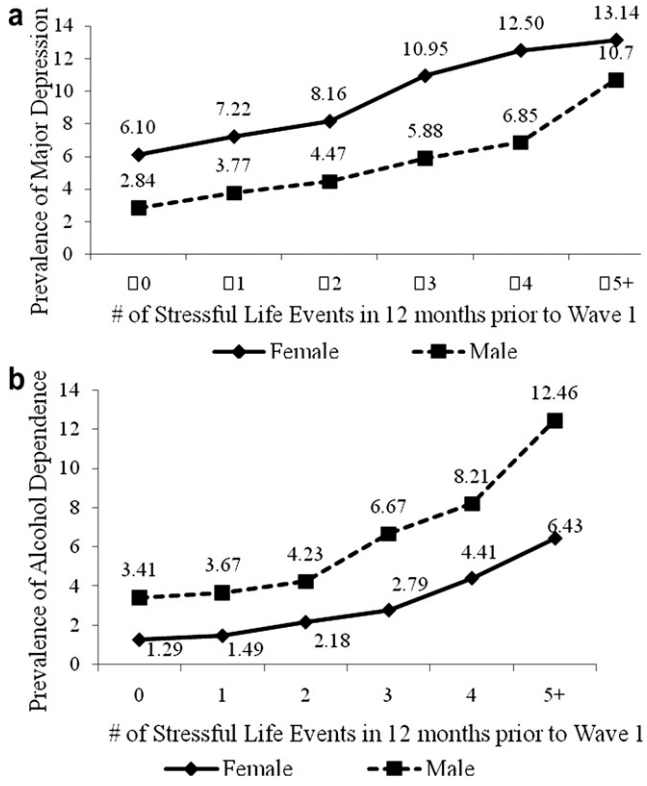

Fig. 1. a. Prevalence of first onset of major depression between Wave 1 and Wave 2 among males and females without a history of major depression at Wave 1 ($N = 27700$) b. Prevalence of first onset of alcohol dependence between Wave 1 and Wave 2 among males and females without a history of alcohol dependence at Wave 1 ($N = 30322$).

consistent with a stress–diathesis model for gender differences in risk for MD and AD.

Cumulative stress and major depression

The associations between gender, MD, and number of stressful life events are presented in the top panel of Table 3. The odds of MD were nearly double for females compared to males (Odds Ratio (OR) = 1.95, 95% CI: 1.71, 2.22). The number of stressful events experienced was significantly associated with higher odds of MD (OR = 1.14 for each additional event, 95% CI: 1.10, 1.20). The interaction between sex and the number of stressful life events (Model 3.a.) was statistically significant (p-value for interaction = 0.047). The odds of MD associated with each additional stressful life event for males was greater compared to the odds for females (OR for males = 1.20, 95% CI: 1.12, 1.29; OR for females = 1.11, 95% CI: 1.05, 1.16). The direction of this sex differences is opposite to our hypothesis, and was unexpected based on the relatively parallel lines observed in Fig. 1a. The difference in the size of the coefficients for males and females is relatively small, but is statistically discernible due to the large size of our sample.

Cumulative stress and alcohol dependence

The bottom panel of Table 3 displays the associations between gender, AD, and number of stressful life events. The odds of AD were approximately double for males compared to females (OR = 1.98, 95% CI: 1.68, 2.34). There was a significant association between the number of stressful life events and the odds of AD (OR = 1.12, 95% CI: 1.06, 1.18). The interaction between sex and the number of stressful life events was not statistically significant ($p = .34$): the OR for AD associated with the number of events for females (OR = 1.16, 95% CI: 1.07, 1.27) was not significantly different from the OR for males (OR = 1.09, 95% CI: 1.02, 1.17) and the direction of trend is opposite to our hypothesis.

Table 4 presents the results of adjusted models for MD and AD fitted for females and males separately, where the number of stressful life events was included as a categorical variable. For both males and females, the odds for MD and AD increased in magnitude with the number of events. The magnitudes of these associations were similar for males and females, with the exception of high stress scores in the prediction of MD (e.g., 5 or more stressors: male OR = 2.89, 95% CI: 1.89, 4.42; female OR = 1.50, 95% CI: 1.06, 2.12). For MD, statistically significant associations were observed for individuals reporting 2 or more stressors relative to individuals who did not report any stressful life events. There was not a significant increase in the odds of AD for males or females reporting 1 to 4 stressors; significant risk was present only among individuals reporting 5 or more stressful life events. In addition, we tested interactions between the categorical stress score and sex,

Table 3
Odds of first onset major depression and first onset alcohol dependence in relation to sex, stressful life events, and the interaction between sex and stressful life events.[a]

Major depression[b]	Model 1.a.	Model 2.a.	Model 3.a.
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Main effects of sex and stress			
Female	1.95 (1.71, 2.22)***	1.94 (1.70, 2.21)***	2.45 (1.83, 3.27)***
Male	1.00	1.00	1.00
Stress Score		1.14 (1.10, 1.20)***	
*Sex*stress interaction*[c]			
			1.11 (1.05, 1.16)**
Stress score for males			1.20 (1.12, 1.29)***
Alcohol dependence[b]	Model 1.b. OR (95% CI)	Model 2.b. OR (95% CI)	Model 3.b. OR (95% CI)
Main effects of sex and stress			
Female	1.00	1.00	1.00
Male	1.98 (1.68, 2.34)***	2.02 (1.71, 2.38)***	2.44 (1.71, 3.48)***
Stress score		1.12 (1.06, 1.18)***	
*Sex*stress interaction*[d]			
			1.16 (1.07, 1.27)**
Stress score for males			1.09 (1.02, 1.17)**

*$p < .05$, **$p < .01$, ***$p < .0001$.
[a] Model adjusted for age, race, poverty ratio, education, marital status, nativity status, and other mood disorders, substance disorders, and anxiety disorders in the 12 months prior to Wave 1.
[b] Males are the reference group in models predicting major depressive disorder, females are the reference group in models predicting alcohol dependence.
[c] There is a significant sex difference in the association between stress and odds of major depression ($p = .047$).
[d] There is not a significant sex difference in the association between stress and odds of alcohol dependence ($p = .23$).

Table 4
Odds of first-onset major depression and first onset alcohol dependence between Wave 1 and Wave 2.[a]

	Major depression ($N = 27700$)		Alcohol dependence ($N = 30322$)	
	Males OR (95% CI)	Females OR (95% CI)	Males OR (95% CI)	Females OR (95% CI)
# of stressors				
0 (ref)	1.00	1.00	1.00	1.00
1	1.27 (0.93, 1.75)	1.13 (0.93, 1.38)	0.95 (0.68, 1.31)	0.99 (0.65, 1.53)
2	1.48 (1.05, 2.09)*	1.28 (1.06, 1.56)*	1.02 (0.74, 1.42)	1.32 (0.92, 1.90)
3	1.74 (1.23, 2.47)**	1.53 (1.20, 1.95)**	1.29 (0.89, 1.86)	1.21 (0.78, 1.86)
4	1.90 (1.19, 3.04)**	1.55 (1.09, 2.20)*	1.40 (0.90, 2.19)	1.59 (0.98, 2.59)
5+	2.89 (1.89, 4.42)***	1.50 (1.06, 2.12)*	1.58 (1.07, 2.34)*	1.90 (1.19, 3.03)*

*$p < .05$, **$p < .01$, ***$p < .0001$.
[a] Model adjusted for age, race, poverty ratio, education, marital status, nativity status, and other mood disorders, substance disorders, and anxiety disorders in the 12 months prior to Wave 1.

and did not find evidence for a sex difference in response to stressful life events for either disorder.

Responsivity to specific types of stress

In secondary analyses, we examined the associations between each of the 12 stressful life events and MD and AD; this was done by fitting 12 logistic models for MD and AD that included a single stressful life event, sex, and their interaction, along with relevant control variables (data not shown). In models predicting MD, only one stressor (financial crisis) exhibited a significant interaction with sex in the prediction of MD, with excess risk for males. In models predicting AD, 3 of the stressors suggested effect modification by sex may be present (report of a family member or friend with a serious illness or injury (excess risk for females); having moved or having someone new move (excess risk for females); and trouble with the police (excess risk for males)). However, after accounting for multiple comparisons (i.e., setting the threshold of statistical significance at $p < .005$ for 12 tests conducted) there was no evidence for statistically significant effect modification by sex for any of the stressful life events in predicting incidence of AD.

The outcome variables in this analysis were first onsets of MD and AD, and individuals with a lifetime history of MD or AD at wave 1 were excluded. As a sensitivity analysis, we examined whether the results would be similar if we included all individuals, including those with a lifetime history of disorder at wave 1. We combined first onsets and recurrent episodes for the outcomes, and reanalyzed the data with statistical adjustment for history of disorder (data not shown). The results of this analysis were largely the same as the results that only considered first onsets.

Discussion

The results of this study are not consistent with a stress–diathesis model as a basis for sex differences in adult onset MD and AD. In this study, stressful life events were not more likely to predict incidence of MD among females compared to males, and were not more likely to predict incidence of AD among males compared to females. Contrary to our expectations, number of stressful life events was more strongly associated with odds of MD for males compared to females, after adjustment for sociodemographic characteristics and other disorders in the year prior to the baseline interview.

Our findings contrast with several prior studies that show a stronger association between stressful life events and depression for females compared to males (Ge, Lorenz, Conger, Elder, & Simons, 1994; Hankin, Mermelstein, & Roesch, 2007; Maciejewski et al., 2001; Nazroo et al., 1997). In addition, our results did not replicate a finding in two prior studies showing greater male sensitivity to the depressogenic effects of divorce or separation (Bruce & Kim, 1992; Kendler et al., 2001). Our failure to show excess female risk for MD following exposure to stressful life events is in agreement with some prior research (Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Turner & Lloyd, 2004); however, we are not aware of any previous reports that have shown a stronger effect of a cumulative stress score in relation to MD for males, as shown in our analysis. We did not observe a significant sex difference in the strength of the association between stressful life events and AD, which is consistent with findings by Lloyd et al. (2008) using a community sample of adolescents. However, this contrasts with previous cross-sectional research using the NESARC data (Dawson et al., 2005) as well as other studies (Perreira & Sloan, 2001; San Jose et al., 2000).

The inconsistencies between our results and studies that have found evidence that stressful events pose differential risk for MD or AD based on sex may be due to methodological differences, including study design, types of stressors considered, and age of participants. Our sample only included individuals ages 18 and older; importantly, our results pertain only to adult first onset of MD and AD and cannot be generalized to recurrent onsets, or episodes of MD or AD that occur before age 18. Data from the National Comorbidity Study Replication shows that the median age of onset for MD is 32 years, and for AD is 23 years (Kessler, Berglund, Demler, Jin, & Walters, 2005); therefore, while our analysis is not able to provide information for a substantial proportion of first onset episodes (i.e., those occurring before age 18), it contributes to knowledge about adult onset disorder, which is a sizeable fraction of those affected by MD and AD. Research suggests that risk factors may differ for juvenile versus adult onset depression (Jaffee et al., 2002), and it is plausible that the determinants of gender disparities are different for adolescent-onset compared to adult onset depression. Therefore, it is important for future research to examine potential determinants of sex differences in MD and AD using both adolescent and adult samples. Finally, it is possible the stress–diathesis model may operate on a continuum that is dependent on the magnitude of the stressors that an individual is exposed to. Our analysis explored number and types of stressors, but it is not sensitive to the magnitude of each stressor, which may be important for research on sex differences in MD and AD.

The results of the present study must be considered within the context of several limitations. Our study is limited by the conceptualization and measurement of stress in the NESARC. We used a 12-item checklist that contained rather broad categories of events; for individuals who endorsed a particular item, we do not have information about the number of times that each type of stressful life event occurred, or contextual details about the event that could be used to assess the impact or burden. Research suggests that consideration of the impact or burden can improve the strength of the associations between stressful life events and

psychological outcomes (Dohrenwend, 2006); our study is limited by the absence of this information. In addition, the list of stressful life events used in this study was not inclusive of all possible stressful life events; therefore, it is possible that sex-specific responses may be present for stressful life events not included in the present inventory, or for a level of detail not collected using this measure. Another limitation is that the NESARC did not collect measures of specific (potential) diathesis factors that may be patterned by sex, such as psychological (e.g., cognitive mechanisms, temperament) or biological (e.g., HPA reactivity, genetic markers) vulnerabilities, which limits the depth of our investigation. Lastly, there was a small amount of attrition between Wave 1 and Wave 2 (13.3%); however, the NESARC sampling weights adjust for non-response due to sociodemographic characteristics and the presence of psychiatric or substance disorder at Wave 1.

This study has several advantages over prior work in testing the differential vulnerability hypothesis as an explanation for sex differences in MD and AD: (1) the sample size was large and representative of the United States population; (2) we employed diagnostic outcomes rather than symptom counts in order to investigate clinically significant outcomes; (3) the sample was measured prospectively, which provided us with confidence about temporal ordering of the stressors with respect to MD and AD; and (4) our outcomes were limited to incident disorders, and therefore provide a focused analysis of predictors of first onset which may differ (in magnitude or quality) from predictors of recurrent disorder.

Conclusions

In conclusion, we did not find empirical support for differential responsivity to stressful life events as an explanation of sex differences in MD and AD. We do not interpret the results of this study as evidence against the involvement of social stressors in sex differences in MD and AD, given that (a) simple checklists of stressors as used in the current study might be too crude of an instrument to detect sex-specific vulnerabilities, and (b) sex (i.e., male versus female)—rather than social, biological, or cognitive characteristics that systematically differ between males and females—may not be a sufficient proxy for understanding sex-based patterning of adult onset MD and AD. Vulnerability toward MD or AD might be contingent on the social context of the events, an individual's subjective appraisal of them, and pre-existing differences in neurobiological stress response pathways. In particular, exploration of contextual variables may be a productive direction for research. Recent evidence from two large multinational comparative studies shows that the gender gap is narrowing for both MD and AD in certain countries (Rahav, Wilsnack, Bloomfield, Gmel, & Kuntsche, 2006; Seedat et al., 2009), and that this narrowing is driven by increases in gender equity and movement away from traditional gender roles.

Sex differences in MD and AD remain one of the most commonly observed findings in psychiatric epidemiology. Our results do not suggest that, at least for adult onset disorders, that sex-specific responsivity to stressors provides substantial explanatory power in understanding the origin of sex differences in these two disorders. These results, along with the inconsistent findings in the literature, indicate the resistance of sex differences to simple explanations. They suggest the need for more nuanced models that incorporate both physiological and social aspects of vulnerability. Mechanisms that bring about sex differences in these disorders should continue to be pursued; this work holds promise for creating an enriched understanding of the etiology of MD and AD, and for the development of strategies to prevent these conditions.

Acknowledgments

This research was supported by a doctoral research award to the first author from the Canadian Institutes of Health Research.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington, DC: American Psychiatric Association.

Aneshensel, C. S., Rutter, C. M., & Lachenbruch, P. A. (1991). Social structure, stress, and mental health: competing conceptual and analytic models. *American Sociological Review, 56*(2), 166–178.

Bleuler, M. (1963). Conception of schizophrenia within the last 50 years and today. *Proceedings of the Royal Society of Medicine-London, 56*(10), 945–952.

Bruce, M. L., & Kim, K. M. (1992). Differences in the effects of divorce on major depression in men and women. *American Journal of Psychiatry, 149*(7), 914–917.

Conger, R. D., Lorenz, F. O., Elder, G. H., Simons, R. L., & Ge, X. O. (1993). Husband-and-wife differences in response to undesirable life events. *Journal of Health and Social Behavior, 34*(1), 71–88.

Dawson, D. A., Grant, B. F., & Ruan, W. J. (2005). The association between stress and drinking: modifying effects of gender and vulnerability. *Alcohol and Alcoholism, 40*(5), 453–460.

Dohrenwend, B. P. (2006). Inventorying stressful life events as risk factors for psychopathology: toward resolution of the problem of in categorical variability. *Psychological Bulletin, 132*(3), 477–495.

Ge, X., Lorenz, F. O., Conger, R. D., Elder, G. H., & Simons, R. L. (1994). Trajectories of stressful life events and depressive symptoms during adolescence. *Developmental Psychology, 30*(4), 467–483.

Grant, B., Kaplan, K., & Stinson, F. (2007). In *Source and accuracy statement: The wave 2 national epidemiologic survey on alcohol and related conditions*. National Institute on Alcohol Abuse and Alcoholism.

Grant, B. F., Dawson, D. A., Stinson, F. S., Chou, P. S., Kay, W., & Pickering, R. (2003). The alcohol use disorder and associated disabilities interview schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug and Alcohol Dependence, 71*(1), 7–16.

Grant, B. F., Goldstein, R. B., Chou, S. P., Huang, B., Stinson, F. S., Dawson, D. A., et al. (2009). Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the wave 2 national epidemiologic survey on alcohol and related conditions. *Molecular Psychiatry, 14*(11), 1051–1066.

Grant, B. F., Kaplan, K., & Moore, T. (2003). In M. D. Bethesda (Ed.), *Source and accuracy statement for Wave 1 of the 2001–2002 national epidemiological survey on alcohol and related conditions*. National Institute on Alcohol Abuse and Alcoholism.

Hankin, B. L., Mermelstein, R., & Roesch, L. (2007). Sex differences in adolescent depression: stress exposure and reactivity models. *Child Development, 78*(1), 279–295.

Hart, K. E., & Fazaa, N. (2004). Life stress events and alcohol misuse: distinguishing contributing stress events from consequential stress events. *Substance Use & Misuse, 39*(9), 1319–1339.

Hasin, D. S., Stinson, F. S., Ogburn, E., & Grant, B. F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States – results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry, 64*(7), 830–842.

Hensing, G., & Spak, F. (2009). Introduction: gendering socio cultural alcohol and drug research. *Alcohol and Alcoholism, 44*(6), 602–606.

Holmila, M., & Raitasalo, K. (2005). Gender differences in drinking: why do they still exist? *Addiction, 100*(12), 1763–1769.

Hyde, J. S., Mezulis, A. H., & Abramson, L. Y. (2008). The ABCs of depression: integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. *Psychological Review, 115*(2), 291–313.

Ingram, R. E., & Luxton, D. D. (2005). Vulnerability-stress models. In B. L. Hankin, & J. R. Z. Abela (Eds.), *Development of psychopathology: A vulnerability-stress perspective* (pp. 32–46). Thousand Oaks, CA: Sage.

Jaffee, S. R., Moffitt, T. E., Caspi, A., Fombonne, E., Poulton, R., & Martin, J. (2002). Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Archives of General Psychiatry, 59*(3), 215–222.

Kendler, K. S., Hettema, J. M., Butera, F., Gardner, C. O., & Prescott, C. A. (2003). Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Archives of General Psychiatry, 60*(8), 789–796.

Kendler, K. S., Thornton, L. M., & Prescott, C. A. (2001). Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. *American Journal of Psychiatry, 158*(4), 587–593.

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology, 48*, 191–214.

Kessler, R. C. (2003). Epidemiology of women and depression. *Journal of Affective Disorders, 74*(1), 5–13.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions' of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 62*(6), 593–602.

Kessler, R. C., & Magee, W. J. (1993). Childhood adversities and adult depression: basic patterns of association in a US national survey. *Psychological Medicine, 23*(3), 679–690.

Lloyd, D. A., & Turner, R. J. (2008). Cumulative lifetime adversities and alcohol dependence in adolescence and young adulthood. *Drug and Alcohol Dependence, 93*(3), 217–226.

Maciejewski, P. K., Prigerson, H. G., & Mazure, C. M. (2001). Sex differences in event-related risk for major depression. *Psychological Medicine, 31*(4), 593–604.

Meehl, P. E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist, 17*(12), 827–838.

Monroe, S. M., & Simons, A. D. (1991). Diathesis stress theories in the context of life stress research: implications for the depressive disorders. *Psychological Bulletin, 110*(3), 406–425.

Nazroo, J. Y., Edwards, A. C., & Brown, G. W. (1997). Gender differences in the onset of depression following a shared life event: a study of couples. *Psychological Medicine, 27*(1), 9–19.

O'Doherty, F. (1991). Is drug use a response to stress? *Drug and Alcohol Dependence, 29*, 97–106.

Perreira, K. M., & Sloan, F. A. (2001). Life events and alcohol consumption among mature adults: a longitudinal analysis. *Journal of Studies on Alcohol, 62*(4), 501–508.

Piccinelli, M., & Wilkinson, G. (2000). Gender differences in depression. Critical review. *British Journal of Psychiatry, 177*, 486–492.

Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry, 149*(8), 999–1010.

Rahav, G., Wilsnack, R., Bloomfield, K., Gmel, G., & Kuntsche, S. (2006). The influence of societal level factors on men's and women's alcohol consumption and alcohol problems. *Alcohol and Alcoholism, 41*, I47–I55.

Rudolph, K. D., Flynn, M., Abaied, J. L., Groot, A., & Thompson, R. (2009). Why is past depression the best predictor of future depression? stress generation as a mechanism of depression continuity in girls. *Journal of Clinical Child and Adolescent Psychology, 38*(4), 473–485.

San Jose, B., Van Oers, H. A. M., Van de Mheen, H. D., Garretsen, H. F. L., & Mackenbach, J. P. (2000). Stressors and alcohol consumption. *Alcohol and Alcoholism, 35*(3), 307–312.

Seedat, S., Scott, K. M., Angermeyer, M. C., Berglund, P., Bromet, E. J., Brugha, T. S., et al. (2009). Cross-national associations between gender and mental disorders in the world health organization world mental health surveys. *Archives of General Psychiatry, 66*(7), 785–795.

Shih, J. H., & Eberhart, N. K. (2008). Understanding the impact of prior depression on stress generation: examining the roles of current depressive symptoms and interpersonal behaviours. *British Journal of Psychology, 99*, 413–426.

Turner, R. J., & Lloyd, D. A. (2004). Stress burden and the lifetime incidence of psychiatric disorder in young adults: racial and ethnic contrasts. *Archives of General Psychiatry, 61*(5), 481–488.

Wilsnack, R. W., Wilsnack, S. C., Kristjanson, A. F., Vogeltanz-Holm, N. D., & Gmel, G. (2009). Gender and alcohol consumption: patterns from the multinational GENACIS project. *Addiction, 104*(9), 1487–1500.

World Health Organization. (2008). *The global burden of disease: 2004 update*. Geneva, Switzerland: World Health Organization.