Childhood adversity interacts with adult stressful events to predict reduced likelihood of smoking cessation among women but not men

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Abstract

Research has documented important sex differences in associations between early stress, stress-sensitization, and psychiatric outcomes. The current study investigated whether sex differences in stress-sensitization extended to cigarette smoking cessation. Data were analyzed from the National Epidemiologic Survey on Alcohol and Related Conditions (waves 1 and 2), selecting for current daily and non-daily smokers at wave 1 (daily smokers: *n*=3,499 women, 3055 men; non-daily smokers: *n*=451 women, 501 men). Three-way interactions between sex, childhood adversity, and past year stressful life events were modeled in the prediction of smoking cessation. Among women, stressful life events were more strongly related to lower likelihood of smoking cessation for those with a history of childhood adversity than those without. This relationship was not found among men. The stress-sensitization model may be applicable to women with regards to smoking cessation, supporting further exploration of stress-sensitization as a prevention and clinical target for smoking cessation.

Keywords

Addictive disorders; Sex Differences; Stress; Child Trauma

Introduction

Experiencing childhood adversity (e.g., childhood abuse, neglect, family substance use) is a highly prevalent and relatively strong risk factor for adverse psychiatric outcomes during adulthood, including substance abuse (Anda, Croft, Felitti, & et al., 1999; Enoch, 2011; Shonkoff et al., 2012; Xie et al., 2011). One mechanism that may explain a portion of the link between childhood adversity and adult substance use is the stress-sensitization model (Hammen, Henry, & Daley, 2000; McLaughlin, Conron, Koenen, & Gilman, 2010). This

model posits that individuals with a history of childhood adversity have greater stress-reactivity and are therefore more sensitive to stress later in life. This heightened sensitivity to stress then increases risk for negative mental health outcomes, such as substance abuse and other psychiatric disorders.

Empirical evidence has supported the hypothesis that stress-sensitization is associated with psychiatric disorder diagnoses, including depression (Hammen et al., 2000; McLaughlin, Conron, et al., 2010) anxiety disorders (Espejo et al., 2007; McLaughlin, Conron, et al., 2010), and alcohol consumption (Young-Wolff, Kendler, & Prescott, 2012). Hammen and colleagues (2000) studied data from a 2-year longitudinal sample of women, finding those with childhood adversity were more likely to have depression at lower levels of current stressful life events than those with less childhood adversity. McLaughlin and colleagues (2010) conducted a similar investigation among a national sample of women and men, and found evidence for stress-sensitization related to the onset of depression and anxiety disorders. At similar levels of childhood adversity, women exhibited greater risk of onset for psychiatric diagnoses at lower levels of past-year stressful life events, suggesting the stress-sensitization effect may have been stronger among women. Young-Wolff and colleagues (2012) studied data from a longitudinal sample of adult twins, and found stressful life events were more strongly predictive of greater alcohol consumption among women with a history of childhood adversity. However, this was only true for events that were rated as independent of the women's own actions (i.e., through a structured interview the researchers surmised the women's own actions did not directly contribute to the occurrence of the stressor).

In addition to depression, anxiety, and alcohol consumption, stress-sensitization may be an important factor related to cigarette smoking cessation among those who experienced childhood adversity, although this topic has yet to be studied. A small number of investigations have found evidence for a positive association between childhood adversity and nicotine dependence. Anda et al. found that those with greater levels of childhood adversity smoked more heavily than those with less childhood adversity (Anda et al., 1999). Likewise, Smith et al. (2013) found childhood adversity was associated with greater levels of nicotine dependence and more severe nicotine withdrawal symptoms among adult smokers (Smith, Homish, Saddleson, Kozlowski, & Giovino, 2013), both important factors related to smoking cessation. There is also evidence that stress and stressful life events are important impediments to smoking cessation, through negative reinforcement mechanisms (Kriegbaum, Larsen, Christensen, Lund, & Osler, 2011; McKee et al., 2011; Nakajima & al'Absi, 2012; VanderVeen et al., 2012). Smokers, particularly women (Weinberger & McKee, 2012), tend to smoke to cope with stress, and are prone to relapse to smoking when faced with stress during a quit attempt. However, there has yet to be a study that examines the interaction between childhood adversity and stressful life events (i.e., stress-sensitization) in relation to smoking cessation.

A comprehensive study of stress-sensitization and smoking should take into account the possibility of sex differences. A number of pre-clinical investigations have found sex differences in neurological and behavioral response to early stress (e.g., Park, Hoang, Belluzzi, & Leslie, 2003; Weinstock, 2007). Weinstock (2007) reported evidence that early

exposure to stress is related to anxiety, depression, and heightened hypothalamic pituitary adrenal axis response in females, compared to reduced hippocampal neurogenesis, LTP, and dendritic spine density in males. In humans, studies have consistently found stronger stress-sensitization effects in relation to psychiatric outcomes among women compared to men (e.g., Young-Wolff et al., 2012; McLaughlin et al., 2010). With regard to smoking, Smith et al. (In press) found childhood adversity was associated with lower likelihood of successfully quitting smoking among women but not men. There is also accumulating evidence that women are more likely than men to smoke in response to stress and negative affect (McKee, Maciejewski, Falba, & Mazure, 2003; Uliaszek et al., 2012; Weinberger & McKee, 2012). Further, when attempting to quit smoking, women exhibit greater levels of negative affect than men (Leventhal et al., 2007). In line with this sex difference, McKee et al. (2003) found that associations between stressful life events (particularly financial events) and transitions in smoking status were stronger among women than men (McKee et al., 2003). Given that smoking in women may be more strongly associated with stress, and given that previous studies have consistently found stress-sensitization to be more strongly related to psychiatric outcomes among women than men, one might also expect stress-sensitization to be more strongly related to lower likelihood of smoking cessation among women than men. This prediction is also consistent with pre-clinical evidence showing that stress during adolescence was associated with locomotor sensitization to nicotine among female, but not male rats (McCormick, Robarts, Gleason, & Kelsey, 2004).

The purpose of this study was to examine longitudinal associations between stress-sensitization and cigarette smoking cessation, using data from a nationally representative sample of U.S. adult cigarette smokers (National Epidemiologic Survey on Alcohol and Related Conditions; waves 1 and 2). We first examined whether childhood adversity and specific subtypes of past year stressful life events (moving/having someone move in with you, financial difficulty, interpersonal violence, interpersonal loss) were related to past year smoking cessation, and whether these associations varied by sex. We then tested the stress-sensitization model in relation to smoking cessation, by examining three-way interactions between sex, childhood adversity, and subtypes of stressful life events. We hypothesized that childhood adversity and past year stressful life events would be associated with lower likelihood of past year smoking cessation among women and men, and that stress-sensitization effects would be more evident among women compared to men.

Method

We analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions, Wave 1 and Wave 2. A detailed account of the NESARC methodology can be found elsewhere (Grant et al., 2009; Grant & Kaplan, 2005; Grant, Kaplan, Shepard, & Moore, 2003; Grant et al., 2004). Briefly, the Wave 1 NESARC data were collected during 2001 and 2002, and Wave 2 during 2004 and 2005. The response rate for Wave 1 was 81%, and the sample of 43,093 represented the civilian, non-institutionalized adult population in the United States. Wave 2 included 34,653 (80%) of the original respondents. For both waves, surveys were administered face-to-face, using computer-assisted personal interviews. African Americans, Hispanics, and young adults were oversampled, and the data were weighted to adjust for non-response at the household and person levels. Based on the 2000

Census, the data were adjusted on socio-demographic variables to ensure an accurate representation of the U.S. population. For the current study, we selected the sample for current smokers at wave 1, who either smoked daily (defined below; n = 3,055 men; n = 3,499 women) or non-daily (n = 501 men; n = 454 women) during the past year. We removed from the sample those who reported smoking cigarettes once per month or less during the past year (n = 186 men; n = 198 women).

Measures

Childhood adversity—Following procedures from McLaughlin et al. (2010), we created a categorical variable based on each respondent's count of childhood adversity subtypes, assessed at Wave 2. These subtypes included physical neglect, emotional neglect, physical abuse, emotional abuse, sexual abuse, family violence, and family adversity (e.g., familial incarceration, familial suicide). Items for each individual subtype were drawn from the Conflict Tactics Scale, the Children's Trauma Questionnaire, and the PTSD section of the NESARC interview. Rather than creating a three-category variable as did McLaughlin et al. (2010), we created a binary variable based on whether the respondent reported any childhood adversity. This was done to ensure adequate sample size for testing interactions with stressful life events (some of which had low prevalence) among the sample of current smokers. Further, too few respondents reported 3 or more types of childhood adversity to generate meaningful results using a continuous count variable for adversity types.

Stress—Past year stressful life events were drawn from two sections of the NESARC interview: the stressful life events checklist and the traumatic events inventory of the posttraumatic stress disorder measure (both collected at Wave 2). Following procedures from McKee et al. (2003), we grouped events into the following categories: residential relocation/had someone come live with you, financial difficulty (fired/laid off from work, unemployed longer than a month, or major financial crisis), and interpersonal loss events (separation/divorce or someone close died). We created an additional category for interpersonal violence/crime victimization, which included physical victimization, sexual victimization, having been stalked, or having had something stolen from you. Unlike McKee et al. (2003), we did not include a category for serious/life threatening accident or illness, due to low endorsement of the item. For each sub-category we generated a binary variable, based on whether the respondent endorsed any of the included items.

Smoking status and cessation—Smokers were defined as those who had smoked 100+ cigarettes in their lifetime and who reported smoking during the past year at wave 1. These smokers were categorized based on their smoking frequency, either daily or non-daily (non-daily ranged from *2 to 3 days per month* to *5 to 6 days per week*). Cessation was defined as daily or non-daily smokers at wave 1 who reported they had not smoked at all during the past year at wave 2.

Covariates—Our covariates included sociodemographics (age, household income, education, and race/ethnicity) all measured at wave 1. Household income was an ordinal variable that ranged from 0 to 21 ("Less than $5,000" to "200,000 or more"). Education was also an ordinal variable that ranged from 1 to 14, "no formal schooling" to "Completed

graduate or professional degree (master's degree or higher)." Race/ethnicity was categorized as White/Caucasian (non-Hispanic or Latino), Black/African American (non-Hispanic or Latino), American Indian/Alaska Native (non-Hispanic or Latino), Asian/Native Hawaiian/ Pacific Islander (non-Hispanic or Latino), and Hispanic or Latino. We also considered including psychiatric diagnoses as covariates in models, including mood disorder, anxiety disorder, substance use disorder, and personality disorder diagnoses, generated using the Alcohol Use Disorder and Associated Disabilities Interview Schedule IV (Grant & Dawson, 2000; Grant, Dawson, et al., 2003). However, these variables had very little impact on study findings and were eliminated in order to estimate the most parsimonious models.

Statistical Analyses

All analyses accounted for the NESARC survey design when calculating estimates, and were conducted using Stata Statistical Software: Release 13.0 (StataCorp, 2013). We first generated descriptive statistics for key study variables, by wave 1 daily vs. non-daily smoking status and by sex. We then tested bivariate associations between our independent variables of interest (childhood adversity, stressful life events) and cessation, with sex interactions to examine sex differences, for each of daily and non-daily smokers. These associations were calculated using logistic regression. Next we separately examined three-way interactions between sex, childhood adversity, and each of the stressful life events categories, adjusting for covariates, for each of daily and non-daily smokers. When three-way interactions were significant, we probed interactions using simple slope analyses. We also examined four-way interactions between sex, childhood adversity, stressful life events, and daily vs. non-daily smoking (at wave 1); however, these analyses may have been underpowered due to small sample sizes in some analysis groups (n < 50). We elected to present both the four-way interaction results as well as three-way interactions between sex, childhood adversity, and stressful life events, stratified by daily vs. non-daily smoking (at wave 1).

In addition to the main analyses, we examined the validity of collapsing childhood adversity into a single variable. We first used confirmatory factor analyses to compute loadings for each type of adversity. We then conducted sensitivity analyses by systematically removing each type of childhood adversity from the binary summary variable and re-computed the models, looking for differences in findings.

Results

Descriptive statistics for key study variables are displayed by sex and daily vs. non-daily smoking status in Table S1 in the Supplemental Material available online. Among daily smokers, women were older (women: mean age = 41.6, SD = 14.9; men: mean = 41.0, SD=14.3; p = 0.010), had slightly higher income (women: mean = 9.1, SD=1.9; men: mean = 9.02, SD = 2.1; p < 0.001), and were less educated (women: mean = 9.3, SD = 4.5; men: mean = 10.1, SD = 4.3; p < 0.001) than men. There was also a significant difference in distribution of race/ethnicity (women: White/Caucasian – 78.2%, Black/African American – 10.4%, American Indian/Alaska Native – 3.7%, Asian/Native Hawaiian/Pacific Island – 1.4%, Hispanic/Latino – 6.2%; men: White/Caucasian – 74.5%, Black/African American –

10.1%, American Indian/Alaska Native – 3.2%, Asian/Native Hawaiian/Pacific Islander – 2.9%, Hispanic/Latino – 9.3%; $p < 0.001$).

Among non-daily smokers, women were older (women: mean = 36.5, SD = 14.9; men: mean = 34.2, SD = 13.2; $p < 0.001$) and had lower education (women: mean = 10.2, SD = 5.0; men: mean = 10.7, SD = 4.7; $p = 0.007$) than men. Women and men did not differ in their reported income (women: mean = 9.7, SD = 2.2; men mean = 9.7, SD = 2.3). The distribution of race/ethnicity significantly differed by sex (women: White/Caucasian – 70.1%, Black/African American – 9.1%, American Indian/Alaska Native – 2.5%, Asian/ Native Hawaiian/Pacific Islander – 3.6%, Hispanic/Latino – 6.2%; men: White/Caucasian – 60.4%, Black/African American – 11.4%, American Indian/Alaska Native – 3.3%, Asian/ Native Hawaiian/Pacific Islander – 4.3%, Hispanic/Latino – 20.6%).

Percentages for stressful life events and childhood adversity were similar between men and women and between daily and non-daily smokers. In other words, greater frequency of smoking (daily vs. non-daily) at wave 1 was not meaningfully associated with childhood adversity or with subsequent stressful life events during the year prior to wave 2. Among daily smokers, 69.5% of women and 71.0% of men reported any childhood adversity. Regarding specific sub-types of adversity, women were substantially more likely to report childhood sexual abuse compared to men (22.1% vs. 6.7%). Interpersonal loss was the most frequently reported stressful life event (42.1% for women and 39.3% for men), while violence/crime victimization was the least frequently reported event (14.2% for women and 14.7% for men).

Among non-daily smokers, 63.1% of women and 69.5% of men reported any childhood adversity. Childhood sexual abuse was more prevalent among women than men (18.8% vs. 5.7%), while physical neglect was more common among men (39.7% vs. 29.1%). For other specific sub-types of abuse, differences were either significant with small effect sizes or non-significant.

There were also minor sociodemographic differences between men and women. Among both daily and non-daily smokers, men had slightly higher education and were more likely to identify as minority race/ethnicity. Other differences were significant but negligible in effect size.

Bivariate associations

Table S2 in the Supplemental Material available online displays bivariate associations between independent variables of interest (childhood adversity, stressful life events) and smoking cessation. Among daily smokers, childhood adversity and all four categories of stressful life events were associated with lower odds of smoking cessation among both men and women ($p < 0.05$). There were two significant sex differences. Having experienced financial difficulty during the past year was more strongly associated with lower odds of cessation among women compared to men (women: $OR = 0.49$, $95\% CI = 0.43, 0.56$; men: $OR = 0.63$, $95\% CI = 0.53, 0.75$; p-value for interaction < 0.05). Having experienced interpersonal violence/crime victimization was also more strongly associated with lower odds of cessation among women compared to men (women: $OR = 0.55$, $95\% CI = 0.48$,

0.63; men: $OR = 0.71$, $95\% CI = 0.60, 0.84$). Among male non-daily smokers, childhood adversity and all experiences of stressful life events were associated with lower odds of smoking cessation. Among women, all associations were also significant, except those for having moved or having someone coming to live with you ($p > 0.05$), and for interpersonal violence/crime victimization ($p > 0.05$). The differences between men and women in associations between these two variables and smoking cessation were statistically significant ($p < 0.05$).

We also computed associations between childhood adversity and stressful life events, for both women and men, and for both daily and non-daily smokers. Among daily smokers, childhood adversity was significantly associated with all types of stressful events, for both men and women. For men, effect sizes ranged from $OR = 1.23$ (for interpersonal loss) to 1.60 (for crime/violence victimization). For women, effect sizes ranged from $OR = 1.21$ (moved/had someone come live with you) to 2.01 (financial difficulty). For non-daily smokers, effect sizes were similar, although not all associations were statistically significant due to smaller sample size.

Adjusted three-way interactions between childhood adversity, stressful life events, and sex

We first tested four-way interactions between childhood adversity, stressful life events, sex, and daily vs. non-daily smoking (at Wave 1). All interactions were non-significant ($p > 0.05$); however, analyses may have been underpowered due to small sample sizes ($n < 50$) in some groups. Rather than combining analyses for daily and non-daily smokers, we elected to present three-way interactions between childhood adversity, stressful life events, and sex stratified by daily vs. non-daily smokers.

Table 1 shows smoking cessation rates by childhood adversity, stressful life events, sex, and daily vs. non-daily smoking (at wave 1). The table also presents the significance of three-way interactions between childhood adversity, stressful life events, and sex after adjusting for covariates, for both daily and non-daily smokers. Among daily smokers, three-way interactions were significant for the following two stressful event types: financial difficulty and interpersonal violence/crime victimization. The interaction was non-significant for experiencing interpersonal loss, and for moving or having had someone come live with you. The interactions for daily smokers are depicted in Figure 1. The interaction between childhood adversity and financial difficulty was significant among women ($p < 0.05$), but not men ($p > 0.05$). For women, financial difficulty was most strongly associated with lower odds of smoking cessation among those with a history of childhood adversity. A similar pattern was found for interpersonal violence/crime victimization: the interaction with childhood adversity was only significant among women, and victimization was most strongly associated with lower odds of cessation among those with a history of childhood adversity.

The interactions for non-daily smokers are depicted in Figure 2. It is important to note that a portion of the cell sizes for the interactions were small (between 15–20 participants), and therefore results should be interpreted with caution. Despite these small samples, the same general pattern of findings was observed when compared to daily smokers: interactions

between childhood adversity and stressful events were most prominently significant among women, and stressful events were more strongly associated with lower rates of cessation for women with childhood adversity than women without. When examining the 3-way interaction between interpersonal loss, childhood adversity, and sex, a pattern emerged whereby there was a clear main effect for childhood adversity – those with childhood adversity were less likely to quit smoking than those without regardless of sex. However, this association between childhood adversity and cessation was stronger among women than men.

Sensitivity analyses

We examined the validity of collapsing childhood adversity types into a single summary binary variable. Confirmatory factor analyses demonstrated each subtype of childhood adversity loaded reasonably well onto a single factor (loadings ranged from 0.38 to 0.70). We then iteratively re-computed the 3-way interaction models, systematically removing and then replacing each subtype of childhood adversity. Although findings were largely consistent regardless of which adversity subtypes were included in the summary variable, there were noteworthy differences.

Among daily smokers, three-way interactions between sex, financial stress, and childhood adversity became non-significant when either emotional neglect or physical abuse were removed from the summary variable. Further probing of the interaction revealed a significant interaction ($p < 0.05$) for financial stress X sex in both cases, whereby financial stress was more strongly associated with lowered rates of smoking cessation for women than men. For example, when emotional neglect was removed from the model, the *OR* for women was 0.50 (*95% CI* = 0.43, 0.57) compared to an *OR* of 0.64 (*95% CI* = 0.54, 0.76) among men.

Among non-daily smokers the three-way interaction between sex, stress related to moving/ having someone come live with you, and childhood adversity was no longer significant when either physical abuse or physical neglect was removed from the adversity summary variable. Further probing revealed that in both cases there was a significant sex by stressful event interaction, whereby moving/having someone come live with you was only associated with lower likelihood of smoking cessation for men. For example, when physical neglect was removed from the summary measure, the OR for moving/having someone come live with you was 0.57 (*95% CI* = 0.44, 0.74) for men and 0.85 (*95% CI* = 0.70, 1.05) for women.

The three-way interaction between sex, childhood adversity, and violence/crime victimization became significant ($p < 0.05$) when physical neglect was removed from the adversity summary variable. Among men, violence/crime victimization was associated with lower odds of smoking cessation among those with no childhood adversity (*OR* = 0.21, *95% CI* = 0.11, 0.40) but not those with childhood adversity (*OR* = 0.14, *95% CI* = 0.80, 1.62). Among women, violence/crime victimization was not significantly associated with lower odds of smoking cessation regardless of childhood adversity ($p > 0.05$).

Consistent with daily smokers, the three-way interaction between financial stress, childhood adversity, and sex became non-significant when emotional neglect was removed from the childhood adversity variable. Further analyses revealed that financial stress was related to lower likelihood of smoking cessation regardless of sex or childhood adversity history (*OR* = 0.61, *95% CI* = 0.53, 0.70).

In summary, in all cases where results from sensitivity analyses differed from the main findings, removal of particular types of adversity removed a significant interaction between childhood adversity and stressful life events for women. Removal of this interaction generated changes to either significant or non-significant three-way interactions between childhood adversity, stressful life events, and sex. These differences resulted when either physical neglect, emotional neglect, physical abuse, or emotional abuse were removed from the models.

Discussion

Results for the interaction between childhood adversity and stressful life events were consistent with a stress-sensitization model for women but not men. Among women, negative associations between stressful life events and smoking cessation were stronger among those with childhood adversity than those without, for two of the four categories among daily smokers (financial difficulty, and interpersonal violence/crime victimization), and three of the four categories among non-daily smokers (moved/had someone come live with you, interpersonal loss, and financial difficulty). Among male daily smokers, none of the interactions between childhood adversity and stressful life events were significant. Among male non-daily smokers, negative associations between violence/crime victimization and cessation were stronger among those *without* childhood adversity than those *with*, which is the opposite of what would be expected based on a stress-sensitization model.

The general pattern of findings, that stress-sensitization was more-so evident among women than men, is consistent with previous literature demonstrating that stress-sensitization is a stronger factor related to substance use and psychiatric co-morbidity for women than men (McLaughlin, Conron, et al., 2010; Young-Wolff et al., 2012). Although these consistent findings point to important sex differences in stress-sensitization and substance use, mechanisms underlying these associations are less clear. Findings to date suggest there are key sex differences in changes to the threat response/stress system resulting from early stressful experiences, which may influence reactions to stressful life events later in life (Weinstock, 2007). Further, these sex differences may be particularly relevant for nicotine sensitivity (Rohleder & Kirschbaum, 2006). Regarding general stress response, exposure to acute and chronic stress can lead to cross-sensitization of stimulant self-administration (including nicotine), related to changes in the dopaminergic system (Cruz, DeLucia, & Planeta, 2008; Cruz, Marin, Leao, & Planeta, 2012; Vezina, 2004). These effects have been demonstrated to be stronger for women than men (Holly, Shimamoto, DeBold, & Miczek, 2012). Regarding early stress, Weinstock (2007) reviewed evidence that prenatal exposure to stress is related to anxiety, depression, and heightened hypothalamic pituitary adrenal (HPA) axis response in female rates, compared to reduced hippocampal neurogenesis, LTP, and dendritic spine density in males. Rohleder and Kirschbaum (2006) reported sex

differences in HPA activity in response to nicotine, with male rats showing activation of plasma arginine vasopressin and female rats showing activation of adrenocorticotropic hormone and corticosterone. There is also direct evidence for sex differences in behavioral responses to nicotine in rats exposed to early stress, with females exhibiting greater locomotive sensitization to nicotine than males (McCormick et al., 2004). Therefore, both increases to the negative and positive reinforcing values of nicotine, as well as the involvement of multiple neurological systems, could potentially play a role in the interplay between sex, childhood adversity, stressful events, and smoking relapse.

It is somewhat unclear why stress-sensitization was not universally evident among women across the different types of stressful events, and for both daily and non-daily smokers. For non-daily smokers, estimates for those without childhood adversity were based on relatively small samples, which may have influenced finings. This was particularly true for interpersonal violence/crime victimization, which is the only type of event for which stress-sensitization was not evident among women. Among female daily smokers, stress-sensitization was not evident for two types of events: 1) having moved or having someone come live with you, and 2) interpersonal loss. The odds ratio for cessation associated with moving/having someone come live with you was 0.83 for women without adversity and 0.68 for those with, which is consistent with stress-sensitization but the difference was not statistically significant. For interpersonal loss, post hoc exploratory analyses (not reported) suggested that stress-sensitization was evident for those reporting divorce/separation, but not those reporting the death of someone close. In the case of death of someone close, the likelihood of cessation was very low regardless of childhood adversity, suggesting the lack of stress-sensitization may be due to the severity of stress involved with the loss of a loved one, regardless of an individual's previous experiences with adversity. In other words, stress-sensitization may be most evident for moderate life-stressors, where associated variability in the likelihood of quitting is greatest.

We did not find evidence for a stress-sensitization effect among men. Others have found a similar pattern of sex differences with regard to depression and alcohol consumption across multiple samples (McLaughlin, Green, et al., 2010; Young-Wolff et al., 2012), supporting the validity of the current findings. It is important to note that sex differences in findings did not appear to be driven by sex differences in types of childhood adversity experienced. Only sexual victimization was more commonly experienced in women than men, and results were the same both with and without victims of childhood sexual abuse in the models (data not shown).

Sensitivity analyses revealed a potentially important pattern of findings, whereby in particular cases physical neglect, emotional neglect, physical abuse, or emotional abuse were responsible for the stress-sensitization effect we had found among women. Most notably, among daily smokers, financial stress was no longer more strongly related to smoking cessation for women with adversity than women without adversity. Taken together, these findings suggest physical and emotional abuse and neglect may be key variables driving sex differences in the stress-sensitization paradigm in relation to smoking cessation.

Limitations

Due to the nature of the questions asked in the NESARC survey, our definitions of smoking cessation was limited to whether respondents reported any smoking during the past year. This likely misclassified some recently quit smokers as current smokers at both waves (those who had quit smoking within a year of the interview), and also likely generated conservative estimates of smoking abstinence. As previously noted, there are many different types of stressful life events that were not captured in our measure. This most likely had the influence of misclassifying some of those with stressful life events as having had none, a misclassification that would have conservatively biased estimates. Our coding of the childhood adversity variable did not take into account potential differences between types of childhood adversity. We elected to operationalize childhood adversity as binary to generate statistically valid and interpretable estimates. However, there may be important differences by sub-types of childhood adversity, and by severity of childhood adversity. An important limitation with regard to interpretation is that we did not have information on quit attempts. Thus, it is not clear whether lower likelihoods of cessation were due to lower likelihood of making quit attempts or lower success during quit attempts. It is also unclear whether differences in cessation were due to differences in treatment seeking, which we were unable to examine in the NESARC data. We theorized that stress-sensitization is the mechanism underlying the study findings, purporting that childhood adversity can lead to greater stress reactivity and this stress reactivity reduced the likelihood of smoking cessation. While we did not have any direct way of assessing stress reactivity, other research has determined that childhood adversity increases stress reactivity (e.g., Chaplin et al., 2014). As stress events and smoking cessation data were collected within the same timeframe (i.e., past year) and are thus cross-sectional, associations may not be causal. For example, it is possible that neurotic personality types may increase the likelihood of reporting childhood adversity, adult stress, and may also contribute to reduced likelihood of cessation. Such third-variable effects cannot be ruled out in the NESARC data. Finally, others have found that the timing of measurement in NESARC (wave 1 vs. wave 2) influences the strength of associations between psychiatric disorders and persistence of substance use disorders (Vergés et al., 2014), raising the concern of measurement bias in the current investigation. In other words, we cannot rule out the possibility that findings may have differed if childhood adversity was measured at wave 1 instead of wave 2.

Conclusions

The current study highlighted substantial variability in the likelihood of smoking cessation based on reported childhood adversity and adult stressful life events for both men and women. The interaction between childhood adversity and stressful life events was more prominently related to variability in cessation for women than men, whereby women with both childhood adversity and stressful life events (financial or interpersonal violence) had the lowest likelihood of smoking cessation. Epidemiological findings from the current investigation do not imply causal relationships, although the results are consistent with a growing body of pre-clinical literature demonstrating the salient role of early stress in the development of nicotine seeking behaviors, as well as evidence for sex differences in these processes.

From a prevention perspective, knowledge of how childhood adversity may influence adult smoking can be used to bolster support for prevention and early secondary interventions targeted at children exposed to maltreatment or high levels of stress. Current secondary interventions typically focus on improving interpersonal relationships, environments, or psychosocial functioning, and have showed early promising results for improving cortisol regulation (see Slopen, McLaughlin, & Shonkoff, 2014 for a review). Future research will be able to determine if these prevention and early intervention efforts modify smoking behaviors in adolescence and adulthood, among other outcomes.

For adolescent and adult smokers, clinical implications of the current findings are difficult to surmise given the infancy of research on this topic. A first step is for investigators to explore whether stressful events and the stress response are differentially related to smoking cessation treatment outcomes for those with or without childhood adversity. These relationships are likely complex, involving interplay with specific types of adversity, specific types of stress, neuro-biological functioning, psychiatric co-morbidity, epigenetic mechanisms, and sex/gender, among other factors. Extensive research would be required to gain a full understanding of the processes. If important relationships do exist, as suggested by pre-clinical and epidemiological findings, it will be important to determine the clinical relevance of these relationships. For example, given that childhood adversity is not a modifiable factor, it will be important to determine if knowledge of this history is clinically relevant, or if understanding male and female smokers' more modifiable, proximal factors (e.g., stress response, psychiatric co-morbidity, neurological functioning, epigenetic functioning) is sufficient for developing personalized cessation treatment. Pharmacological interventions for smoking that address the stress response are currently being developed (McKee et al., 2014), and may be particularly beneficial to smokers with a history of childhood adversity.

Acknowledgments

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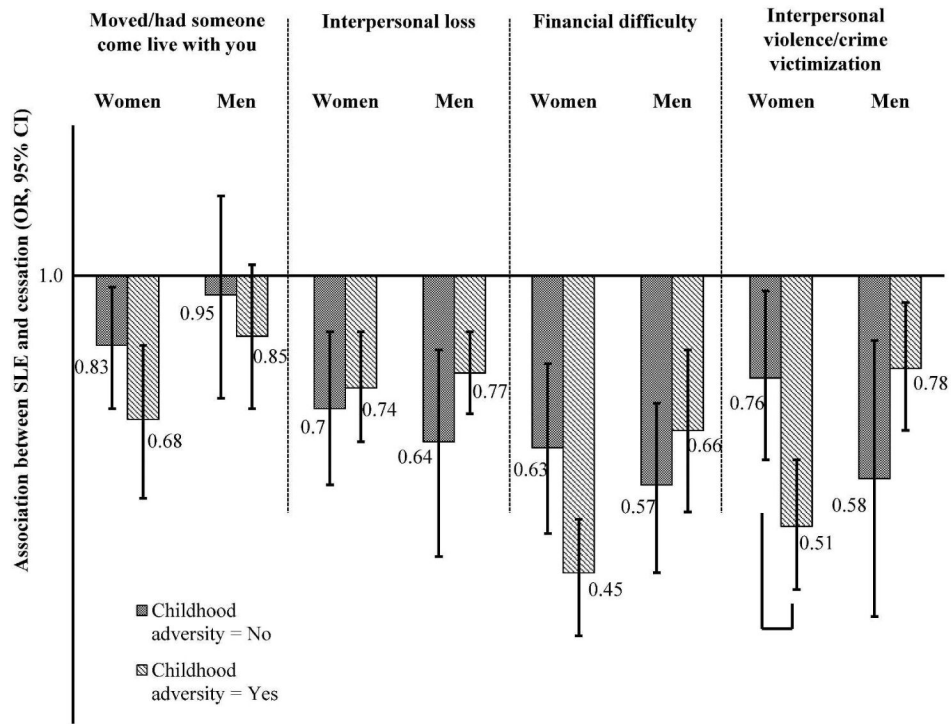
Figure 1. Daily smokers

sex differences in the interaction between past year stressful life events (SLE; wave 2) and childhood adversity (measured at wave 2), predicting smoking cessation by wave 2. Estimates accounted for the survey design, and were adjusted for age, income, education, and race/ethnicity (all measured at wave 1).

Figure 2. Non-daily smokers

sex differences in the interaction between past year stressful life events (SLE; wave 2) and childhood adversity (measured at wave 2), predicting smoking cessation by wave 2. Estimates accounted for the survey design, and were adjusted for age, income, education, and race/ethnicity (all measured at wave 1).
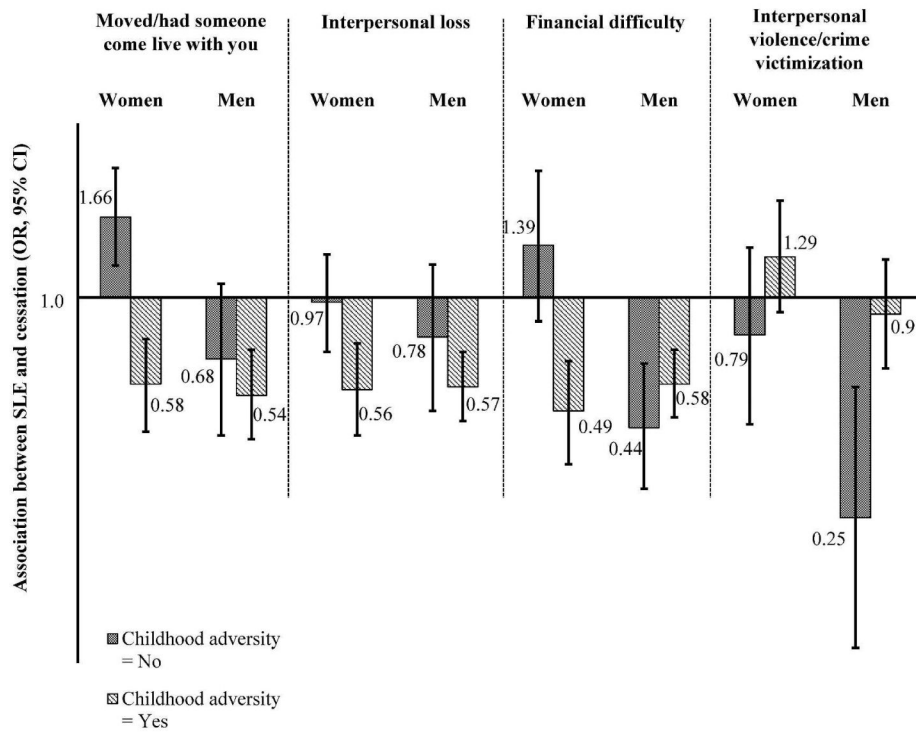
Table 1

Adjusted three-way interactions between sex, childhood adversity, and stressful life events

| | Men | | | | Women | | | | 3-way interaction OR(95% CI) |
| | CA = No | | CA = Yes | | CA = No | | CA = Yes | | |
	Total n	% Quit	Total n	% Quit	Total n	% Quit	Total n	% Quit	
Past year daily smokers [a]									
Stressful event									
Moved/had someone come live with you [c]									
No	673	17.37	1,653	13.96	763	18.99	1,769	15.20	0.91(0.61, 1.36)
Yes	173	16.60	554	12.14	254	16.27	710	10.89	
Financial difficulty [c]									
No	652	18.99	1,524	14.93	768	19.85	1,498	17.19	0.61(0.43, 0.87)**
Yes	196	11.80	683	10.42	251	13.48	982	8.53	
Interpersonal loss [c]									
No	537	19.40	1,291	14.55	642	20.16	1,335	15.52	0.85(0.53, 1.37)
Yes	311	13.46	916	12.03	377	15.07	1,145	12.03	
Interpersonal violence/crime victimization [c]									
No	754	17.95	1,840	13.96	913	18.70	2,048	15.02	0.50(0.30, 0.83)**
Yes	94	18.70	367	11.29	106	14.98	432	8.32	
Past year non-daily smokers [a]									
Stressful event									
Moved/had someone come live with you [c]									
No	168	54.59	340	49.83	156	47.49	302	49.55	0.43(0.22, 0.85)*
Yes	45	45.09	134	35.32	54	59.83	140	36.32	
Financial difficulty [c]									
No	160	57.35	349	48.57	163	49.00	307	51.06	0.27(0.13, 0.53)***
Yes	53	37.54	125	35.57	47	56.99	135	33.92	
Interpersonal loss [c]									0.79(0.40, 1.55)

| | Men | | | | Women | | | | |
| | CA = No | | CA = Yes | | CA = No | | CA = Yes | | 3-way interaction OR(95% CI) |
	Total n	% Quit	Total n	% Quit	Total n	% Quit	Total n	% Quit	
No	156	54.09	286	50.88	139	51.06	259	50.39	
Yes	57	47.91	188	36.52	71	50.23	183	36.52	
Interpersonal violence/crime victimization [c]									
No	192	56.08	402	45.56	185	51.25	378	44.75	0.47(0.16, 1.36)
Yes	21	24.89	72	43.03	25	45.34	64	51.09	

Note: All estimates accounted for the NESARC survey design. Estimates adjusted for age, income, education, and race/ethnicity.

*
$p < .05,$

**
$p < .01,$

***
$p < .001.$

[a] Measured at wave 1.

[b] Measured at wave 2.

[c] Past year occurrence, measured at wave 2.