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Associations of Gender, Smoking, and Stress with Transitions in Major Depression Diagnoses

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Using data from the newly available U.S. National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Wave 3; *n* = 36,309), we evaluated relationships among gender, cigarette smoking status (current, former, non-smoker), life event stress (0-1 vs. 2+ events), and their impact on transitions in major depression diagnosis (MDD†; new vs. absent cases; ongoing vs. remit cases). Women who were both current and former cigarette smokers with more than two stressful events had higher rates of new MDD diagnosis compared to men who were current or former smokers with two or more stressful events. Current smoking and experiencing two or more stressful events increased the odds of having an ongoing MDD diagnosis, while being a former smoker decreased these odds. Results suggest that smoking and stress are markers for depression risk in women and should help guide clinical assessment as well as gender-difference research on the biological underpinnings of these conditions.

INTRODUCTION

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders in the United States [1], with a 12-month prevalence of 5.3 percent and a lifetime prevalence of 16.6 percent [2,3]. The comorbidity between MDD and smoking is well-established in the neurobiological, epidemiological, and clinical literature. Longitudinal studies indicate that depressive-like symptoms are associated with the onset of smoking initiation [4], and adults diagnosed with MDD often report higher rates of smoking [5] and reduced ability to quit smoking [6]. In a nationally representative sample (National Epidemiologic Survey on Alcohol and Related Conditions; NESARC, Wave 1 and 2), current and lifetime MDD were associated with a higher likelihood of continued smoking, lower rates of quitting smoking, and higher rates of smoking relapse [7]. Similarly, smokers are more likely to have higher rates of MDD, report greater depression symptoms, and have more depressive episodes than their non-smoker counterparts [5,6,8].

Prior research demonstrates important interplay between smoking, stressful life events, and major depression. For example, life event stress increases the risk of major depression [9,10], particularly in women [11]. Stress and negative affect are also associated with the initiation, maintenance of, and relapse to smoking [4]. Likewise, depressive symptoms and anxiety are associated with a higher risk for smoking initiation [12], and nicotine dependent individuals demonstrate higher rates of MDD and anxiety disorders [13]. Preclinical literature demonstrates that the dysregulation of the nicotinic acetylcholine receptor (nAChR) system, the primary target of nicotine, is associated with increased negative affect and depression [14,15]. Clinically, stimulation of the cholinergic system leads to an increase in anxiety-like behavior and depressive symptoms in individuals with

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†Abbreviations: MDD, Major Depression Disorder; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; nAChR, nicotinic acetylcholine receptor.

Keywords: Depression, MDD, Smoking, Stress, Gender Differences

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mood disorders [16]. Taken together, findings suggest an intricate association between smoking behavior and stressful life events on the development and maintenance of MDD diagnoses.

With regard to gender, a significant amount of research has consistently demonstrated greater prevalence of MDD in women compared to men in the U.S. and other countries [2,3,17,18], and associations between MDD and smoking are stronger in women compared to men [19]. Women are also more likely to report smoking for negative affect regulation [20,21], to improve mood [22], and to reduce negative affective symptoms [23]. Following a negative mood induction, women have shorter latencies to smoke than males [24], and females with more accessible beliefs that smoking will reduce negative affect smoked more cigarettes with greater puff duration and volume [25]. In contrast, men may be more likely to smoke for the reinforcing properties of nicotine, whereas nicotine reinforcement may play a diminished role in maintaining tobacco use in women [26-31]. Given that depression is twice as common in women as in men in U.S. data [32] and associations between major depression, smoking, and stress are stronger in women compared to men, smoking and stress are likely to affect transitions in MDD diagnoses, and these associations may be greater in women than in men.

The purpose of this study was to examine associations among gender, cigarette smoking, and stressful life events in association with transitions of Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (*DSM*-V) MDD diagnoses, using newly available data from a nationally representative sample of adults living in the United States (National Epidemiologic Survey on Alcohol and Related Conditions; Wave 3). We first examined whether cigarette smoking (current, former, non-smoker) and stressful life events in the past 12 months were related to 1) new vs. absent cases of depression in the past 12 months and 2) ongoing vs. remitted cases of depression in the past 12 months, and whether these associations varied by gender. We then examined two- and three-way interactions, in relation to major depression diagnoses (new vs. absent; ongoing vs. remit), between gender, cigarette smoking, and stressful life events. We hypothesized that current cigarette smoking and stressful life events would be associated with a greater likelihood of new or ongoing cases of major depression, and that these relationships would be more evident in women compared to men. Specifically, we hypothesized that female, current cigarette smokers with stressful life events would be most likely to have a new MDD diagnosis, and would also to be less likely to remit a MDD diagnosis.

METHODS

Data Source

The cross-sectional NESARC study (Wave 3, 2012-2013) was carried out by the National Institute on Alcohol Abuse and Alcoholism. Personal interviews were conducted with 36,309 non-institutionalized civilians aged 18 and older living in the United States. Hispanic, African American, and Asian respondents were oversampled. Data were adjusted for oversampling and non-response, then weighted to represent the US civilian population. NESARC methodology used in the Wave 3 NESARC survey are detailed elsewhere [33,34].

Stressful Life Events

Wave 3 of the NESARC survey included questions regarding 16 stressful events occurring in the last 12 months prior to the Wave 3 interview. Items assessed stress related to moving, job loss or instability, loss of relationships (divorce, death), interpersonal conflict, financial difficulties, legal difficulties, or being a victim of a crime (e.g. *Have you moved or has anyone new came to live with you in the last 12 months?; Were you fired or laid off from a job in the last 12 months?*). The total number of stressful life events were calculated based on answers to the 16 stressful events questions. Given that the distribution of stressful life events was positively skewed, we used a median split to create two groups (0 or 1 events vs. two or more events). Prior work assessing stressful life events has utilized a median split to characterize stressful life events with this scale [35,36].

Cigarette Smoking Status

Cigarette smoking status was characterized by the following: *current users* reported having smoked cigarettes in the last 12 months, *former users* reported *not* having smoked cigarettes in the last 12 months, and *non-smokers* reported never having smoked cigarettes and were non-users of any other tobacco or nicotine product (i.e., cigars, pipe, chew/snuff, e-cigarettes).

Major Depression

Wave 3 of the NESARC survey used *DSM*-V criteria to determine diagnostic status [37]. We coded the NESARC data into the following categories for past 12-month diagnoses. *Absent*: No diagnosis in the past 12 months and no diagnosis 13 to 24 months prior to the interview. *New*: Diagnosis in the past 12 months but no diagnosis 13 to 24 months prior to the interview. *Remit*: No diagnosis in the past 12 months but diagnosis 13 to 24 months prior to the interview. *Ongoing*: Diagnosis in the past 12 months and diagnosis 13 to 24 months prior to the interview.

Analysis

All analyses were weighted and accounted for the NESARC survey design when calculating estimates with

Table 1. Sample characteristics by gender.

	Men	Women	$\chi 2$	*p*
Age (%)			5.24	.07
18-29	22.8	21.8		
30-44	27.5	28.2		
45+	49.7	49.9		
Race/Ethnicity (%)			37.98	<.0001
Caucasian	52.7	52.2		
African American	20.3	22.4		
Native American	1.3	1.5		
Asian	5.6	4.7		
Hispanic	20.1	19.3		
Household income (%)			227.65	<.0001
$9,999 or less	9	10.9		
$10,000 - $24,999	22.6	27.7		
$25,000 - $49,999	27.9	27.8		
Over $50,000	40.5	33.6		
Education (%)			44.6	<.0001
Less than high school	16	14.7		
Completed high school	28.4	26.1		
Some college or higher	55.6	59.2		
Marital status (%)			648.41	<.0001
Married	41.8	38.1		
Living with a partner	6.9	5.9		
Widowed	3.7	9.8		
Divorced	13	15.6		
Separated	3.5	5		
Never married	30.9	25.6		
Cigarette smoking status (%)			684.44	<.0001
Current	30.3	21.6		
Former	19.9	14.5		
Non-user	49.9	63.8		
***DSM*-V major depression diagnosis (%)^**			523.41	<.0001
Absent	83.6	73.3		
New	0.9	1.8		
Remit	7.6	12.1		
Ongoing	8	12.8		
Stress (%)			0.42	.52
0 or 1 events	57.8	58.2		
2 or more events	42.2	41.8		

Note: ^past 12 months; *Absent*, no diagnosis in the past 12 months and no diagnosis prior to the past 12 months;
New, diagnosis in the past 12 months but no diagnosis prior to the past 12 months;
Remit, no diagnosis in the past 12 months but diagnosis prior to the past 12 months;
Ongoing, diagnosis in the past 12 months and diagnosis prior to the past 12 months.

SAS software (SAS v9.4, SAS Institute Inc., Cary, NC). Binary logistic regression analysis was used to examine associations between cigarette smoking (current, former, non-smoker), stressful life events (0 or 1 vs. two or more events), gender, and transitions in *DSM*-V MDD diagnoses (absent vs. new; remit vs. ongoing). Relationships between cigarette smoking, stressful life events, and gender were assessed in terms of odds ratios. The effects of each variable of interest on any given outcome were interpreted relative to our chosen reference outcome (i.e., non-smoker, 0 or 1 stressful life events, male). Two- and three-way interactions between cigarette smoking, stressful life events, and gender for absent versus new cases of depression and remit versus ongoing cases of depression were performed to investigate whether cigarette smoking, stress, and gender was associated with transitions in MDD diagnoses. Significant three-way interactions were further examined with z-tests of proportions for cells where expected values differed from observed values. Secondary analysis examined associations between all tobacco/e-cigarette use (current, former, non-user) and the pattern of results was the same as cigarette smokers. The sample size was insufficient to examine each type of tobacco use (except cigarettes) separately. Supplementary sensitivity analysis determined that outcomes were similar for those with 0 or 1 stress events, and different from those experiencing two or more stress events. Age, race, income, education, and marital status were evaluated as potential

Table 2. Percent new versus absent MDD and percent ongoing versus remitted MDD by cigarette smoking status, life event stress (0 or 1 events and 2+ events), and gender (n = 35,120).

Female

	Current Smokers		Former Smokers		Non-smokers	
	0 or 1 event	2+ events	0 or 1 event	2+ events	0 or 1 event	2+ events
Depression *n*(%)						
Absent	1324 (98.4)	1421 (94.2)	1404 (99.0)	603 (95.1)	6829 (99.0)	3275 (95.9)
New	21 (1.6)	87 (5.8)	14 (1.0)	31 (4.9)	70 (1.0)	139 (4.1)
Remit	207 (46.9)	387 (35.4)	303 (62.9)	200 (48.9)	712 (59.2)	633 (44.7)
Ongoing	234 (53.1)	705 (64.6)	179 (37.1)	209 (51.1)	490 (40.8)	784 (55.3)

Male

	Current Smokers		Former Smokers		Non-smokers	
	0 or 1 event	2+ events	0 or 1 event	2+ events	0 or 1 event	2+ events
Depression *n*(%)						
Absent	1670 (99.8)	1873 (97.2)	1771 (99.2)	687 (99.0)	4187 (99.6)	2231 (98.3)
New	3 (0.2)	54 (2.8)	14 (0.8)	7 (1.0)	17 (0.4)	39 (1.7)
Remit	123 (46.1)	241 (38.3)	159 (62.8)	119 (54.6)	242 (58.9)	239 (45.4)
Ongoing	144 (53.9)	389 (61.7)	94 (37.2)	99 (45.4)	169 (41.1)	288 (54.6)

covariates. As they had no impact on the pattern of results, they were removed from the final models.

RESULTS

Sample characteristics by gender are summarized in Table 1. All chi-square analyses that were performed to examine gender differences were significant at $p < .001$, except age ($p = .07$) and stress ($p = .65$). New, remitted, or ongoing cases of MDD were each more prevalent in women compared to men. Men were more likely to report having an absent MDD diagnosis. Current and former cigarette smoking were more prevalent in men compared to women. Women were more likely to report never having used cigarettes.

New Cases of MDD vs. Absent Cases of MDD

New cases of MDD were significantly associated with gender, cigarette smoking status, and stress (all p's < .001). Females (OR = 2.57), current cigarette smoking (OR =1.49), and two or more stressful life events (OR = 4.38) were associated with greater odds of new MDD. New MDD demonstrated a significant gender by smoking status by stress three-way interaction ($p = .02$). Female, current cigarette smokers with two or more stressful life events had greater rates of new MDD compared to males who were current smokers with two or more stressful life events (5.8% vs. 2.8%; z = 4.35, $p < .0005$). Female, former cigarette smokers with two or more stressful life events had greater rates of new MDD compared to males who were formers smokers with two or more stressful life events (4.9% vs. 1%; z = 4.23, $p < .0005$) (see Tables 2 and 3).

Ongoing Cases of MDD vs. Remitted Cases of MDD

Ongoing MDD was significantly associated with cigarette smoking status and stress (all p's < .0001). Current cigarette smoking (OR = 1.63) and two or more stressful life events (OR = 1.72) were associated with greater odds of ongoing MDD, while former cigarette smoking (OR = .85) was associated with lower odds of an ongoing MDD diagnosis. Two- and three-way interactions were not clinically significant (see Tables 2 and 3).

DISCUSSION

To our knowledge, this is the first study to examine the relationship between gender, cigarette smoking, and stressful life events in association with transitions in *DSM*-V MDD diagnoses from a newly released dataset of a nationally representative sample of adults in the United States. Results from the interaction between gender, smoking status, and stressful life events in new versus absent MDD diagnoses newly identify that females who were both current and former cigarette smokers with two or more stressful life events were more likely than males who were current or formers smokers with two or more stressful life events to have a new MDD diagnosis. New depression diagnoses in women were more commonly comorbid with current (6 percent) and former (5 percent) cigarette smoking and two or more stressful life events. In comparison, men with two or more stressful life events who were current or former smokers had rates of new depression at 3 percent and 1 percent, respectively.

Females (OR = 2.57), current (vs. non-smoker) cigarette smoking (OR = 1.49), and those with two or more stressful life events (OR = 4.38) were more likely to have

Table 3. Odds ratios (OR) for main effects and interactions between gender, cigarette smoking status, and stress for new vs. absent cases of MDD and ongoing vs. remit cases of MDD (n = 35,120).

	New vs. Absent		Ongoing vs. Remit
Main effects		**Main effects**	
Gender		Gender	
(Wald=66.24, p<.0001)		(ns)	
Female	2.57 (2.05, 3.23)	Female	ns
Male	ref.	Male	ref.
Cigarette smoking status		Cigarette smoking status	
(Wald=14.87, p=.0006)		(Wald=61.97, p<.0001)	
Current	1.49 (1.20, 1.84)	Current	1.63 (1.40, 1.89)
Former	ns	Former	0.85 (0.72, 0.99)
Non-smoker	ref.	Non-smoker	ref.
Stress		Stress	
(Wald=109.07, p<.0001)		(Wald=75.59, p<.0001)	
2 or more stressful life events	4.38 (3.32, 5.78)	2 or more stressful life events	1.72 (1.52, 1.94)
0 or 1 stressful life events	ref.	0 or 1 stressful life events	ref.
2-way interaction		**2-way interaction**	
Gender by Smoking status (ns)		Gender by Smoking status (ns)	
Smoking status by Stress (ns)		Smoking status by Stress (ns)	
Gender by Stress (ns)		Gender by Stress (ns)	
3-way interaction		**3-way interaction**	
Gender by Smoking status by Stress		Gender by Smoking status by Stress	
(Wald=7.62, p=.02)		(ns)	

Note: versus (vs.); reference (ref.); not significant (ns)

new MDD versus absent MDD. This is consistent with prior findings indicating that both smoking [6] and stress [9] increase risk of major depression, and that this risk is greater in females compared to males [17]. It is well-established that females are more likely to smoke to manage affect and stress [20-22], and our findings suggest that women who were current or former cigarette smokers with two or more stressful life events were more likely to be newly identified with depression than men with similar smoking behavior and two or more stressful life events. These findings point to important gender differences in the association of smoking status, stress, and transitions to new depression diagnoses.

Among individuals with ongoing MDD diagnoses, current (vs. non-smoker) cigarette smoking (OR = 1.63) and two or more stressful life events (OR = 1.72) were more prominently associated with ongoing MDD versus remitted MDD. Our results suggest that current cigarette smoking and higher stress levels may be a marker for depression, and that these markers may not necessarily be gender-specific in cases of ongoing depression. Again, these results are consistent with findings that smokers often have higher rates of MDD [5,6,8] and life event stressors increase risk of depression [9,11]. Former (vs. non-smoker) cigarette smoking (OR = .85) was associated with lower odds of an ongoing MDD diagnosis. This finding is in agreement with a recent study demonstrating that quitting smoking reduced the risk of MDD [38]. Therefore, successfully quitting smoking at some prior time may be 'protective' and related to better mental health prognoses. Though causal relationships must be interpreted with caution given the cross-sectional nature of our findings, it can be hypothesized that ongoing depression may be maintained by smoking and stress in both men and women, and that interventions targeting the motivation to quit smoking may be of therapeutic benefit for depression. Evidence exists to support that mental health outcomes, including depression, anxiety and stress indicators, improve following smoking cessation [39].

Overall, these findings are consistent with the hypercholinergic hypothesis of depression [14,40]. This hypothesis posits that hyperactivation of the cholinergic system and associated increases in acetylcholine release may lead to depression. Nicotine activates nAChRs within the cholinergic system and influences multiple neurotransmitter systems (e.g., serotonin, norepinephrine), impacting on the modulation of depression and the stress response [7,14]. Prior work has demonstrated that chronic nicotine exposure desensitizes nAchRs thereby reducing cholinergic activation. Indeed, dysregulation of the cholinergic system has been associated with increased negative affect and depression [14]. Thus, dysregulated cholinergic activity may contribute to the development and maintenance of MDD, and smoking may be an attempt to regulate this system. It has been posited that smokers may self-medicate depressive-like symptoms by desensitizing their nAchRs [14]. Based on the current findings, we hypothesize that women may have greater cholinergic dysregulation than men thus accounting for the strong associations between smoking and two or more stressful life events in women transitioning to a new MDD diagnosis. This is consistent with preclinical findings demon-

strating that female mice are less sensitive to the psychostimulant properties of nicotine, and that chronic nicotine exposure increases anxiety-like behavior in female versus male mice [41]. The authors of that study suggest that this finding may be related to higher relapse rates in women following abstinence. Although not examined in the current investigation, menstrual cycle phase may play a role in moderating smoking behavior and stress in women transitioning to a new MDD diagnosis.

LIMITATIONS

First, the assessment of cigarette smoking status and stressful life events were limited to the 12 months prior to the NESARC Wave 3 interview. The present investigation cannot address the causal or temporal relationship between cigarette smoking status, life event stress, and major depression. For example, it is possible that having a depression diagnosis may increase the odds of cigarette smoking and higher stressful life events. Second, stressful life events relied on retrospective recall and the NESARC survey did not address the severity of life event stress. Severity ratings can inform whether any particular stressful life event was more strongly associated with MDD than others. Similarly, many types of stressful life events were not addressed in the NESARC survey. This could lead to individuals being misclassified into having had none or little stressful life events when it is plausible that they could have experienced a stressor(s) not addressed in the NESARC survey. Fourth, prior work suggests a moderating role of coping on perceived impact of life events on stress outcomes. Measuring stress by assessing number of stressful life events occurring in the last 12 months may not fully capture the impact of coping on life event stressors. Further, cigarette smoking status was assessed for the past year, creating the potential for misclassification whereby some were no longer smoking at the time of the interview. Finally, while the NESARC survey included information on cigarettes smoked per day, duration of smoking, and tobacco use disorder diagnoses, only past 12-month smoking status was examined in our analysis of associations between gender, smoking status, and stress with transitions in MDD diagnoses.

CONCLUSIONS

The interaction between gender, cigarette smoking status, and stress for new versus absent *DSM*-V MDD was more prominently related to new MDD diagnoses in women, whereby women who were current or former smokers with stress had the highest likelihood of new MDD in the past 12 months. Smoking status and two or more stressful life events were also more prominently related to ongoing MDD diagnoses, whereby current cigarette smoking and two or more stressful life events were independently and strongly related to ongoing MDD diagnoses. Epidemiological findings from the present investigation do not imply causal or temporal relationships, although the results are consistent with the well-established literature base demonstrating that women are more likely to smoke to manage stress and cope with depression, and smoking and stress increase risk for depression, particularly in women. Our results suggest that smoking and stress may be markers for depression, particularly in women, and, as such, should guide clinical assessment as well as gender-difference research on the biological underpinnings of these conditions. From a prevention perspective, knowledge on how gender, smoking status, and stressful life events influence transitions in MDD diagnoses could be helpful for preventive care strategies and patient support.

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