Journal of Consulting and Clinical Psychology
2006, Vol. 74, No. 1, 186–190

0022-006X/06/$12.00 DOI: 10.1037/0022-006X.74.1.186

Posttraumatic Stress Disorder and Late-Onset Smoking in the Vietnam Era Twin Registry

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Epidemiological and clinical studies have consistently reported associations between smoking and posttraumatic stress disorder (PTSD). This study analyzed diagnostic interview data on 6,744 members of the Vietnam Era Twin Registry to clarify the PTSD–smoking relation and to examine whether genetic liability for smoking moderated this relation. Preexisting active (unremitted) PTSD increased risk of late-onset daily smoking. Remitted PTSD decreased risk. Active PTSD increased risk of smoking at all levels of genetic liability; the effect was strongest for those with least genetic liability. This suggests PTSD represents a nongenetic pathway to late-onset smoking among individuals who were nonsmokers prior to developing PTSD. If replicated, these results identify PTSD as a risk factor for smoking that should lead to early tobacco control treatment in this population.

Keywords: posttraumatic stress disorder, smoking, twins, genetic, veterans

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A version of this article was presented at the annual meeting of the Society for Research on Nicotine and Tobacco in Prague, Czechoslovakia, in March 2005. Karestan C. Koenen is supported in part by National Institute of Mental Health (NIMH) Grant K08MH070627. Brian Hitsman is supported in part by National Institute on Drug Abuse (NIDA) Grant K08DA017145. Laura Stroud is supported in part by NIMH Grant K23MH65443. This work was also funded in part by the National Cancer Institute Transdisciplinary Tobacco Use Research Center Grant P50 CA 84719. Additional funding was provided by the NIDA and by the Robert Wood Johnson Foundation. The United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry.

Numerous organizations have provided invaluable assistance in the conduct of this study, including the Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University. Most important, we gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution, this research would not have been possible.

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Epidemiological and clinical studies have reported an association between smoking and posttraumatic stress disorder (PTSD; Beckham, 1999; Breslau, Novak, & Kessler, 2004; Lasser et al., 2000). The prevalence of current smoking among individuals with PTSD is 45.3%, almost double the prevalence in the general population (Lasser et al., 2000). Increased smoking among Manhattan residents following September 11, 2001, was associated with higher risk for PTSD (Vlahov et al., 2002). Using data from the National Comorbidity Survey, Breslau, Davis, and Schultz (2003) showed that both past PTSD, which had remitted before daily smoking began, and active PTSD (not remitted) were associated with a twofold increased risk of daily smoking. Taken together, these findings support a robust PTSD–smoking association.

The present study uses data from an epidemiological sample of 3,372 male–male twin pairs from the Vietnam Era Twin (VET) Registry to further examine the nature of this association. The first goal of this study was to test whether PTSD increases risk of daily smoking after we controlled for shared risk factors unaccounted for in previous studies. Following the lead of Breslau et al. (2004), we divided preexisting PTSD into active and past. We then extended their analyses by adjusting for demographic factors, military service factors, and other preexisting mental disorders. Demographic factors such as low socioeconomic status are associated with increased risk of PTSD (Kulka et al., 1990) and of daily smoking (Gilman, Abrams, & Buka, 2003). Severity of combat exposure, which strongly predicts PTSD, may be independently associated with risk for daily smoking (Stellman, Stellman, & Sommer, 1988). Alcohol dependence and major depression are associated with both PTSD and daily smoking (Breslau et al., 2003; 2004; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995).

The second goal of the present study was to test whether the PTSD–smoking association was moderated by level of genetic liability to smoking. It is well-known that smoking is highly heritable (Yoshimasu & Kioyohara, 2003). To our knowledge, the question of whether the PTSD–smoking relation differs by level of genetic liability to smoking has not been examined. We proposed competing hypotheses for this analysis. PTSD may only increase risk of smoking among those at high genetic risk. Alternatively, PTSD may provide an alternative, nongenetic, pathway to smoking. That is, individuals at high genetic liability may smoke whether or not they have PTSD; PTSD may increase risk of smoking only among those at low levels of genetic liability.

Method

Sample

Participants were drawn from the VET Registry. The VET Registry is a nationally distributed cohort consisting of male–male twin pairs born between 1939 and 1957 in which both siblings served on active military duty during the Vietnam War era (Eisen, True, Goldberg, Henderson, & Robinette, 1987). Zygosity was determined using a questionnaire and blood group typing methodology that achieved 95% accuracy (Eisen et al., 1987). Registry members are representative of all twins who served in the military during the Vietnam War on a variety of sociodemographic and other variables (Eisen, Neuman, Goldberg, Rice, & True, 1989; Goldberg, True, Eisen, & Henderson, 1987; Henderson et al., 1990). The data used in the present study were from the 1987 Survey of Health and the Harvard Twin Study of Drug Abuse and Dependence (1991–1992, Tsuang, Bar, Harley, & Lyons, 2001). The response rate was 79.6%. The mean age of respondents was 44.6 years ($SD = 2.8$, range = 36–55 years); 90.4% were non-Hispanic White, 4.9% were African American, 2.7% were Hispanic, 1.3% were Native American, and 0.7% were "Other." One third reported high school as their highest degree attained, and 38.6% were college graduates; 92.6% were employed full-time and 1.8% part-time. At the time of the study, 75% had been married and 11% were never married. Registry members lived in all 50 states of the United States. The majority of participants were monozygotic (MZ) twins (55.6%).

Measures

Age of entry into the military and education at entry into the military were abstracted from military records. Southeast Asia (SEA) service status and combat exposure level were from the 1987 Survey of Health. Demographic information; parental psychopathology data; and lifetime diagnoses of PTSD, conduct disorder (CD), alcohol and drug abuse and dependence (A–D), and major depression (MD) were obtained as part of the 1992 Harvard Twin Study of Drug Abuse and Dependence using the Mental Health Diagnostic Interview Schedule (Version III—rev.; DIS–III–R; Robins, Helzer, Cottler, & Golding, 1988). The DIS–III–R is a structured psychiatric interview for epidemiological research leads to clinical diagnoses based on the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.; American Psychiatric Association, 1987). Lifetime daily smokers were defined as those who responded affirmatively to the question "Did you ever smoke cigarettes daily for a month or more?" and the age of onset was defined as the earliest age they met this criterion for daily smoking. For diagnoses, the age of onset was defined as the earliest onset of symptoms for those meeting lifetime criteria for a disorder. Of veterans who reported experiencing a traumatic event, 35% reported combat as their worst event. Other details of the interview procedure, types of traumatic events reported, and PTSD diagnostic data were reported previously (Koenen et al., 2002). Reliability of diagnoses of the twins was assessed by reinterviewing a subset of 146 participants using a different interviewer at a mean interval between interviews of 466 days ($\pm$50.5). The test and retest reliabilities for participants in the present study for PTSD ($\kappa = 0.40$), CD ($\kappa = 0.46$), MD ($\kappa = 0.76$), alcohol A–D ($\kappa = 0.76$), and drug A–D ($\kappa = 0.71$) were in the fair to good range (Slutske et al., 1998). These reliability estimates are similar to those found in other community samples with low base rates of diagnoses. Reliabilities for retrospectively reported ages of onsets were good to excellent (ranging from $r = .98$ for PTSD to $r = .62$ for alcohol A–D). Severity of combat exposure was measured using the Combat Exposure Index (Janes, Goldberg, Eisen, True, & Henderson, 1992), which asks each veteran whether he or she engaged in 18 specific combat activities, such receiving incoming fire. An index of combat exposure was constructed by summing positive responses. The index demonstrated good internal consistency ($\alpha = .86$) and test–retest reliability ($\kappa = 0.84$). Its validity is supported by a strong association with being awarded a military combat medal.

Statistical Analysis

Because members of a twin pair are from the same family, analyses were conducted using the sandwich variance estimator to correct for nonindependence (Kohler & Rodgers, 2001). Cox proportional hazards models with time-dependent covariates were used to estimate the hazards ratio (HR) for time of initiation of daily smoking. The HR is defined as risk of time to an outcome for those with and without a specified risk factor (Collett, 1999). Time-dependent covariates were used because they allow the status of certain independent variables (e.g., PTSD, other mental disorders) to change over time and thereby account for temporal ordering of onset. Only PTSD occurring before daily smoking contributes to risk of daily smoking. Time was indicated by chronological age. Participants who were not daily smokers by the time of the interview were censored at their age at the time of interview. That is, because survival analysis uses time-to-event data, participants who had not started smoking by the interview contributed time as a nonsmoker equal to their age in years at the interview.

Temporality of time-dependent covariates and daily smoking could not be determined if they began in the same year. Observations with onsets occurring in the same year were censored at 1 year earlier (Chilcoat & Breslau, 1998). This approach was followed because of uncertainty about the temporal ordering of the observations. Models were estimated using the XTCOX procedure in Stata, Version 7.0 (Stata Corporation, 2001). PTSD and other psychiatric disorders were defined as preexisting if the first onset of the disorder occurred before the year of smoking onset. Preexisting PTSD was defined as a combination of the two groups classified as active if the symptoms of the disorder continued through the age of onset of daily smoking or past (remitted) if the symptoms of the disorder were last experienced 1 year or more before smoking onset.

Does PTSD uniquely increase risk of late-onset daily smoking? We estimated two Cox models for the outcome of daily smoking. The first model estimated the risk for daily smoking in persons with preexisting PTSD, relative to individuals exposed to trauma who had not developed PTSD. The second model estimated the risk for daily smoking in persons with active or past PTSD relative to individuals exposed to trauma who had not developed PTSD. To examine the unique association between PTSD and daily smoking, each model adjusted for demographic and military service factors and then adjusted in addition for preexisting psychiatric disorders. Demographic and military service factors included those significantly associated with PTSD and smoking in previous work with this sample (Koenen et al., 2002) and/or in the literature (Niaura & Abrams, 2002) such as zygosity, minority race, father did not graduate high school, mother did not graduate high school, maternal–paternal depression–alcohol problems–drug problems–problems with the law, Vietnam service, age of entry into the military, education less than high school at entry into the military, and combat exposure severity.

Is the PTSD–daily smoking association moderated by genetic liability to daily smoking? We examined whether the PTSD–daily smoking association was moderated by genetic liability. Previous research suggested that additive genetic influences explain the majority of the variance in daily smoking (Yoshimasu & Kioyohara, 2003). Given these findings, twins were assigned to one of four categories of "genetic liability" to daily smoking based on their cotwin's lifetime history of daily smoking as follows: (a) lowest risk, MZ twin and cotwin never daily smoker; (b) low risk, dizygotic (DZ) twin and cotwin never daily smoker; (c) medium risk, DZ twin and cotwin lifetime daily smoker; (d) high risk, MZ twin and cotwin lifetime daily smoker. Following the lead of other investigators (Kendler et al., 1995), we coded the four groups proportionally as −1.0, −0.5, 0.5, and 1.0, respectively. We tested whether the PTSD–smoking association was moderated by genetic liability to smoking using survival analysis. The model included a main effect term for PTSD, a term for genetic liability, and a term for the interaction of PTSD and genetic liability. Demographic factors, military service, and other preexisting mental disorders were included as covariates. A significant interaction term indicated that the effect of PTSD on risk for smoking was moderated by genetic risk.

Results

A total of 3,065 participants, constituting 46% of the sample, reported exposure to one or more traumatic events, of which 649 (21%) received lifetime diagnoses of PTSD. There were 4,439 participants (66%) with a lifetime history of daily smoking. The prevalence of trauma exposure and PTSD did not differ for MZ versus DZ twin pairs. The prevalence of daily smoking was slightly lower in MZ pairs (64%) than DZ (68%) pairs. Zygosity prevalence differences were adjusted for in the analyses.

The average age of onset of daily smoking was 17.8 (SD = 3.3, mode = 18), which is earlier than the average age of onset for PTSD (M = 24.0, SD = 7.8, mode = 20). Among those with lifetime PTSD (n = 649), 20% (n = 131) never smoked, 57% (n = 370) started smoking before PTSD onset, and 23% (n = 148) started smoking at the same time or after PTSD onset. The average age of onset of daily smoking for those who started at the same time or after PTSD onset was 19.2 (SD = 3.1), almost 3 years later than the average age (M = 16.4, SD = 2.9) for those who started smoking before PTSD onset. Therefore, in the analyses reported in this article, we tested whether PTSD increases risk of late-onset daily smoking—that is, smoking that begins well after the average age of risk in this sample.

Does PTSD Uniquely Increase Risk of Late-Onset Daily Smoking?

The lifetime prevalence of daily smoking was elevated (80%) among those with lifetime PTSD as compared with those exposed to trauma who did not develop PTSD (69%), $\chi^2(1, N = 3065) = 29.45$, $p < .001$. The first column of Table 1 presents the unadjusted HR of daily smoking in those with PTSD (preexisting, active, or past) as compared with the trauma exposed without PTSD. The second and third columns present the HR adjusted for demographic and service factors and preexisting psychiatric disorders, respectively. Active PTSD was associated with significantly increased risk of daily smoking in all models. Past PTSD

Table 1
Relative Hazard Ratios (and 95% CIs) of Late-Onset Daily Smoking by PTSD Status

Predictor	Unadjusted	Adjusted for demographic & military service factors[a]	Adjusted for preexisting psychiatric disorders[b]
Preexisting PTSD[c]	1.17 (0.96, 1.41)	0.95 (0.76, 1.17)	1.03 (0.83, 1.27)
Past PTSD[c]	0.71 (0.54, 0.94)*	0.57 (0.42, 0.76)***	0.60 (0.45, 0.80)***
Active PTSD[c]	2.69 (1.22, 3.28)***	2.36 (1.86, 2.98)***	2.71 (2.06, 3.57)***

Note. N = 3,065 trauma-exposed veterans. CI = confidence interval; PTSD = posttraumatic stress disorder.
[a] Estimates of hazard ratios for PTSD are adjusted for zygosity, minority race, father did not graduate high school, mother did not graduate high school, maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, maternal/paternal problems with the law, Vietnam service, age of entry into the military, education less than high school at entry into the military and combat exposure. [b] Preexisting disorder is defined as first onset at least 1 year before onset of PTSD. Preexisting disorders include conduct disorder, major depression and alcohol/drug abuse or dependence. [c] Preexisting PTSD combines active and past PTSD. Past PTSD is defined by remittance at least 1 year prior to the onset of daily smoking. Active PTSD represents ongoing PTSD symptoms during year of onset of daily smoking.
* $p < .05$. *** $p < .001$.

was associated with significantly decreased risk. Prevalence data further illustrate this; although the prevalence of daily smoking was increased among those with active PTSD (98%) versus the trauma exposed without PTSD (71%), the prevalence was much less among those with past PTSD (26%). We hypothesized that the contrasting effects of active versus past PTSD on risk of daily smoking may be due to differences in age of onset and duration of symptoms. Active PTSD had a significantly ($p < .001$) earlier age of onset ($M = 16.74$, $SD = 4.60$) than past PTSD ($M = 25.23$, $SD = 8.26$). Active PTSD was also characterized by a significantly ($p < .001$) longer period from age of disorder onset to age at last symptom ($M = 17.80$ years, $SD = 9.44$) as compared with past PTSD ($M = 10.29$ years, $SD = 9.28$).

Is the PTSD–Daily Smoking Association Moderated by Genetic Liability to Daily Smoking?

Table 2 presents the estimates for risk of late-onset daily smoking by PTSD and genetic liability. Level of genetic liability was highly predictive of daily smoking. The main effect term for active PTSD and the interaction term for Active PTSD × Genetic Liability to Smoking were both significantly associated with increased risk of daily smoking. The main effect term for past PTSD was associated with significantly decreased risk of daily smoking; the interaction of past PTSD and genetic liability was not significant. The significant interaction term for Active PTSD × Genetic Liability indicates the active PTSD–daily smoking association was stronger at lower levels of genetic liability than at higher levels. This is illustrated in Table 3, which presents the effect of active PTSD on risk of daily smoking stratified by genetic liability. Although active PTSD is associated with increased risk of late-onset daily smoking at all levels of genetic liability, it has a larger association with daily smoking among those at lower genetic liability than among those at high genetic liability.

Discussion

We found that active PTSD was associated with an increased risk of late-onset daily smoking, a finding consistent with that of Breslau et al. (2004). The magnitude of risk associated with active PTSD was greater than twofold, after we controlled for a wide range of potential confounders not accounted for in previous research, including parental education, parental psychiatric history, military service characteristics, combat exposure severity, and other psychiatric disorders. Active PTSD was associated with increased risk of late-onset smoking at all levels of genetic liability; however, the effect on risk was stronger for those at low genetic liability than for those at high genetic liability. This suggests PTSD may present an alternative nongenetic pathway to late-onset daily smoking for veterans whose genetic and family backgrounds otherwise place them at low risk of ever smoking.

We were unable to determine from these data why individuals with active PTSD are more likely to become daily smokers. Clinical studies of Vietnam veterans suggest that smoking is related to avoidance and hyperarousal symptoms (Beckham et al., 1997). Kassel, Stroud, and Paronis (2003) suggested a biological mechanism consistent with our findings. Animal models indicate that early stress may prime dopaminergic pathways, making nicotine more reinforcing and increasing risk of smoking initiation (Kassel et al., 2003). Genetic liability to smoking may also operate through these dopaminergic pathways (Li, Ma, & Beuten, 2004). We speculate that the relatively early onset (average age of 17 years), very chronic form of active PTSD in this sample sensitized dopaminergic pathways, making veterans more vulnerable to the reinforcing effects of nicotine. This effect was strongest among veterans at low genetic liability, as their reinforcement pathways had not already been genetically sensitized to reinforcement.

Remitted PTSD was associated with decreased risk of daily smoking in this sample, a finding in contrast to that of Breslau et al. (2004). The very high base prevalence of daily smoking (66%) as well as relatively late onset (average age of 25 years) and long duration (10 years) of remitted PTSD in our sample may explain these contrasting findings. The age of 25 is past the age of initiation for daily smoking; 98% of daily smokers in our sample had already started smoking by age 25, and almost 100% had started by age 35. Although our definition of past PTSD was modeled after that of Breslau et al. (2004), our data were such that

Table 2
Adjusted Relative Hazards of Late-Onset Daily Smoking by Trauma, PTSD and Level of Genetic Liability

Predictor	Hazard ratio[a] (95% CI)	$\chi^2(1)$
Active PTSD[b]	3.68 (2.93, 4.63)***	123.64***
Past PTSD[b]	0.60 (0.42, 0.84)**	9.01**
Genetic risk	2.10 (1.91, 2.30)***	254.51***
Active PTSD × Genetic Liability	0.39 (0.30, 0.50)***	53.12***
Past PTSD × Genetic Liability	0.84 (0.51, 1.40)	0.46

Note. $N = 3{,}065$ trauma-exposed veterans. CI = confidence interval; PTSD = posttraumatic stress disorder.
[a] Estimates of hazard ratios for PTSD are adjusted for zygosity, minority race, father did not graduate high school, mother did not graduate high school, maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, maternal/paternal problems with the law, age at entry into the military, education at entry into the military, combat exposure, and preexisting mental disorders. [b] Past PTSD is defined by remittance at least 1 year prior to the onset of daily smoking. Active PTSD represents ongoing PTSD symptoms during year of onset of daily smoking.
** $p < .01$. *** $p < .001$.

Table 3
Adjusted Relative Hazard Ratios (and 95% CIs) of Late-Onset Daily Smoking by Active PTSD Status, Stratified by Level of Genetic Liability

Level of genetic liability	Hazard ratio[a] of daily smoking by active PTSD[b]
Lowest	8.48 (5.45, 13.21)***
Low medium	6.44 (3.42, 12.12)***
High medium	2.52 (1.83, 3.46)***
Highest	1.57 (1.20, 2.05)***

Note. $N = 3{,}065$ trauma-exposed veterans. CI = confidence interval; PTSD = posttraumatic stress disorder.
[a] Estimates of hazard ratios for PTSD are adjusted for zygosity, minority race, father did not graduate high school, mother did not graduate high school, maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, maternal/paternal problems with the law, age at entry into the military, education at entry into the military, combat exposure, and preexisting mental disorders. [b] Active PTSD represents ongoing PTSD symptoms during year of onset of daily smoking.
*** $p < .001$.

past PTSD could, by definition, only have predicted the very rare event of very late onset daily smoking.

Generalization from our findings is limited by our sample of male Vietnam era veterans and may not extend to civilians or women. However, over one million men are currently in active duty in the U.S. armed forces (U.S. Department of Defense, 2000), and active duty military personnel are at high risk for trauma exposure. Because of the recent conflicts in Iraq and Afghanistan, the prevalence of combat exposure and risk of PTSD among military personnel are increasing (Hoge et al., 2004). Thus, understanding the PTSD–smoking relation among male military personnel remains an important public health goal. A further limitation is that the reliability of PTSD diagnosis in our sample is only fair, although it is similar to that found in other epidemiologic samples. This would be expected to result in misclassification related to PTSD diagnosis, diluting differences between PTSD and no-PTSD groups and biasing our results toward the null hypothesis.

Our study, like that of Breslau et al. (2004), found that active PTSD increases risk of daily smoking. These findings are based on recall and should be replicated prospectively. If replicated, they identify PTSD as a risk factor for daily smoking that should lead to early tobacco control treatment in this population.

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Received November 10, 2004
Revision received July 21, 2005
Accepted July 27, 2005 ■