

# A Twin Registry Study of the Relationship Between Posttraumatic Stress Disorder and Nicotine Dependence in Men

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**Context:** Recent studies indicate a strong association between posttraumatic stress disorder (PTSD) and nicotine dependence (ND). However, the explanation for the association remains unclear.

**Objective:** To test competing explanations for the association between PTSD and ND.

**Design, Setting, and Participants:** Analysis of data on 6744 members of the Vietnam Era Twin Registry, a national registry of all male-male twin pairs who served in the military during the Vietnam era interviewed in 1991-1992.

**Main Outcome Measures:** Risk of PTSD and ND using the Diagnostic Interview Schedule for the *DSM-III-R*.

**Results:** The prevalence of ND was elevated among trauma-exposed individuals (52.0%) and those with PTSD (71.7%) compared with unexposed individuals (40.5%). This association was significant for ND and for trauma without PTSD (odds ratio, 1.31; 95% confidence interval [CI], 1.18-1.45) and for PTSD (odds ratio, 2.34; 95% CI, 1.92-2.84) and was not entirely explained by shared risk fac-

tors. Shared genetic effects explained 63% of the PTSD-ND association; the remaining covariance was explained by individual-specific environmental effects. Using survival analysis with time-dependent covariates, ND was associated with a substantially increased risk of PTSD among trauma-exposed men (hazard ratio, 1.98; 95% CI, 1.61-2.42). Trauma (hazard ratio, 1.49; 95% CI, 1.35-1.64) and PTSD (hazard ratio, 1.36; 95% CI, 1.14-1.61) were less strongly but significantly associated with increased risk of ND onset after controlling for shared risk factors.

**Conclusions:** Most of the PTSD-ND association is explained by shared genetic effects. However, there is a substantial, robust PTSD-ND association not explained by shared risk factors. Multiple explanations for the association were supported; however, the strongest association was consistent with preexisting ND increasing the risk of PTSD onset. These data suggest that male veterans with a history of ND may be at increased risk for PTSD. Further research on the biological mechanisms underlying PTSD-ND comorbidity is needed.

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**E**PIDEMIOLOGIC AND CLINICAL studies have reported associations between smoking and posttraumatic stress disorder (PTSD).<sup>1-6</sup> Although smoking is highly addictive, the relationship between PTSD and nicotine dependence (ND) has received less attention. Nicotine dependence is defined by a cluster of cognitive, behavioral, and physiologic symptoms that indicate that an individual persists with smoking despite experiencing significant smoking-related problems. This article considers 4 alternative explanations for the association between PTSD and ND. First, PTSD could be a causal risk factor for ND in that individuals with PTSD might use nicotine to cope with subjective stress. Incidence data suggest that PTSD increases the risk

of ND.<sup>7</sup> Second, ND, through its association with high-risk lifestyles, could indirectly increase the risk of PTSD by increasing the risk of trauma exposure, a criterion for the diagnosis of PTSD. Third, among individuals who experience trauma, ND could increase the risk of PTSD. The possibility that high levels of nicotine use could have neurobiologic effects that increase vulnerability to PTSD has received little attention to date.<sup>8</sup> Fourth, the association between ND and PTSD may be due to shared vulnerability factors that increase the risk of both disorders.

Many potential shared vulnerability factors exist. Exposure to trauma, which is required for the diagnosis of PTSD, is independently associated with the risk of ND.<sup>7</sup> Preexisting conduct disorder (CD), major depression (MD), and alcohol and

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drug abuse/dependence (A/D) are associated with increased risk of PTSD,<sup>9-11</sup> and ND is highly comorbid with these disorders. Shared familial vulnerability may also play a role. Genetic effects explain a substantial proportion of the variance in smoking and ND<sup>12-14</sup> as well as in PTSD.<sup>15,16</sup> Shared genetic effects partially explain the comorbidity between both disorders and alcohol and drug A/D.<sup>17-21</sup> A family history of antisocial behavior is associated with an increased risk of trauma and PTSD,<sup>11,22,23</sup> and ND is associated with an underlying vulnerability to disinhibitory behavior.<sup>24</sup> Previous research did not examine shared familial vulnerability as an explanation for the PTSD-ND relationship.

Twin studies offer a natural experiment that can be used to test whether shared familial vulnerability accounts for the relationship between 2 phenotypes, such as PTSD and ND.<sup>25</sup> The twin method exploits the different levels of genetic relatedness between monozygotic (MZ) and dizygotic (DZ) twin pairs to estimate the contributions of genetic and environmental factors to individual differences in the outcome of interest.<sup>26</sup> Population covariance between PTSD and ND may be partitioned into an additive genetic component and 2 types of environmental components. The first is a common environmental effect that is correlated between twins and has made siblings similar to each other. The second is an individual-specific environmental effect that is uncorrelated between siblings and includes measurement error. Once familial (genetic or common environmental) effects on the PTSD-ND association have been accounted for, the hypothesis that there are significant individual-specific environmental effects can also be tested. If a causal relationship between phenotypes exists, individual-specific environmental effects on the association between phenotypes should be significant.<sup>27</sup> However, the classic twin method has only limited ability to inform us as to the direction of this relationship.<sup>28,29</sup>

The present study combines twin and epidemiologic methods to test alternative explanations for the PTSD-ND association in the 6744 members of the Vietnam Era Twin (VET) Registry. The epidemiologic methods used were proposed by Chilcoat and Breslau<sup>30</sup> to disentangle the directional relationships between PTSD and substance use disorders. Although our data do not permit us to establish a causal relationship between PTSD and ND, testing competing etiologic hypotheses can improve our understanding of their association. Because association and temporal precedence are 2 prerequisites to a causal relationship, we focus on these to clarify which causal models are viable.

We first examined the PTSD-ND association and tested whether the association was accounted for by shared risk factors, including familial (genetic or environmental) vulnerability. Once we established the presence of a significant, robust PTSD-ND association, we used information on the temporal ordering of disorder onset to examine the direction of the association. Our analyses addressed 4 etiologic questions: (1) Is trauma exposure in the absence of PTSD associated with increased risk of subsequent ND onset? (2) Is PTSD associated with increased risk of subsequent ND onset? (3) Is preexisting ND associated with increased risk of subsequent exposure to traumatic events?

(4) Is preexisting ND associated with increased risk of subsequent PTSD onset after a traumatic event?

## METHODS

### SAMPLE

Participants were drawn from the VET Registry, 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 era.<sup>31</sup> Zygosity was determined using a questionnaire and blood group typing method that achieved 95% accuracy.<sup>32</sup> The VET Registry members are representative of all twins who served in the military during the Vietnam era regarding a variety of sociodemographic and other variables.<sup>31,33,34</sup> The data used in the present study are from the Harvard Twin Study of Drug Abuse and Dependence (1991-1992). The response rate was 79.6%. The mean  $\pm$  SD age of the respondents was  $44.6 \pm 2.8$  years (range, 36-55 years); 90.4% were non-Hispanic white, 4.9% were African American, 2.7% were Hispanic, 1.3% were American Indian, and 0.7% were "other." Approximately one third of the participants reported high school as their highest degree attained, and 38.6% were college graduates. Regarding employment, 92.6% of the respondents worked full-time and 1.8% part-time. Seventy-five percent of the participants had been married at the time of the study, and 11% were never married. Registry members lived in all 50 states of the United States. Because the VET Registry includes only male-male twin pairs, most participants were MZ twins (55.6%).

### MEASURES

Age at entry into the military, education at entry into the military, and Southeast Asia service were abstracted from military records. Demographic information, parental psychiatric data, and lifetime diagnoses of PTSD, ND, CD, alcohol and drug A/D, and MD were obtained using the National Institute of Mental Health Diagnostic Interview Schedule Version III—Revised,<sup>35</sup> which is a structured psychiatric interview for epidemiologic research leads to clinical diagnoses based on the *DSM-III-R*.<sup>36</sup> Details of the interview procedure, types of traumatic events reported, and PTSD diagnostic data were reported previously.<sup>11</sup> Approximately 35% of the veterans reporting trauma exposure cited combat as their worst trauma. Reliability of diagnoses of the twins was assessed by another interview of a subset of 146 participants using a different interviewer, with a mean  $\pm$  SD interval between interviews of  $466.0 \pm 50.5$  days. The test and retest reliabilities for participants in the present analysis for ND ( $\kappa = 0.73$ ), 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.<sup>37,38</sup> These reliability estimates are similar to those found in other community samples with low base rates of diagnoses. Reliabilities for retrospectively reported ages at onset were good to excellent, ranging from  $r = 0.62$  for alcohol A/D to  $r = 0.98$  for PTSD.

The categorical variables maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, and maternal/paternal problems with the law were created based on the co-twin's response to a series of questions, eg, "Did your mother/father have problems with depression/alcohol/drugs/the law?" asked about each parent separately. Co-twin report of parental problems was used to construct the parental psychiatric variables to reduce the potential impact of index twin psychiatric symptoms on variables representing the functioning of his parents. Combat exposure was measured using a combat exposure index,<sup>39</sup> which asks each veteran whether he engaged in 18 specific combat activities, such as flying in

an attack helicopter and receiving incoming fire. A global index of combat exposure was constructed by summing all positive responses from an individual. The global index is used to classify combat exposure into 5 ordinal categories: 0, did not serve in Southeast Asia; 1, served in Southeast Asia but did not experience combat; 2 to 3, low combat; 4 to 6, medium combat; and 7 or more, high combat. The ordinal combat categories demonstrated good internal consistency (Cronbach  $\alpha = .86$ ) and test-retest reliability ( $\kappa = 0.84$ ). The validity of the index is supported by a strong association between the combat exposure index and being awarded a military combat medal.

## STATISTICAL ANALYSIS

Because all respondents were included, all phenotypic analyses were conducted using the sandwich variance estimator to correct for the nonindependence of data from respondents in the same family.<sup>40,41</sup>

### Association and Shared Risk Factor Analyses

Logistic regression analyses were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between ND and trauma exposure without PTSD and for ND and PTSD among trauma-exposed individuals. We then tested whether the association could be explained by shared risk factors by entering these into the logistic regression models. Potential shared risk factors were those significantly associated with trauma/PTSD and ND in previous work with this sample<sup>11,22</sup> or in the literature<sup>42,43</sup> and included minority race, paternal education less than high school graduation, maternal education less than high school graduation, maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, maternal/paternal problems with the law, Vietnam service, age at entry into the military, education less than high school graduation at entry into the military, and preexisting CD, MD, and alcohol and drug A/D. Combat exposure was included in the model for the association between ND and PTSD. If, after adding these variables, the PTSD-ND OR is attenuated to nonsignificance, the relationship is accounted for by 1 or more shared risk factors.

### Twin Method: Test of Shared Familial Vulnerability

We first computed tetrachoric correlations for MZ and DZ pairs to measure twin pair similarity for PTSD and ND. The tetrachoric correlation assumes that a continuous, normally distributed latent liability underlies the observed dichotomous distribution of diagnosis. It estimates the correlation between the underlying liability distribution rather than the observed dichotomous variables.

We then tested whether the PTSD-ND association was accounted for by shared familial vulnerability by using Mx software<sup>44,45</sup> and maximum likelihood estimation techniques to fit different structural equations to raw data. Because trauma exposure is a criterion for the diagnosis of PTSD, veterans who did not report trauma exposure were coded as missing. In the univariate twin model, the variance for PTSD or ND is partitioned into the variance due to additive genetic (A), common environmental (C), and individual-specific environmental (E) effects. In the bivariate twin analysis, MZ and DZ correlations are compared across traits, that is, one twin's PTSD diagnosis is correlated with the co-twin's ND diagnosis. If the cross-trait twin correlations are greater for MZ than for DZ twins, this implies that genetic factors contribute to the phenotypic correlation between the 2 traits. A genetic correlation ( $r_A$ ) indicates the extent to which genetic effects on one trait

overlap with those on the second trait. A common environmental correlation ( $r_C$ ) indicates the extent to which common environmental effects on one trait also affect the second trait. An individual-specific environmental correlation ( $r_E$ ) indicates the extent to which individual-specific environmental effects on one trait also affect the second trait. A significant  $r_E$  indicates that the association between phenotypes is not accounted for by shared genetic or common environmental factors. A significant  $r_E$  is consistent with a causal relationship between traits<sup>27</sup> or environmental risk factors uncorrelated between siblings and may include measurement error.

When conducting model fitting to raw data in Mx, the  $\chi^2$  goodness-of-fit statistic is calculated by subtracting the log-likelihood of the fitted model from the log-likelihood of the observed data under a saturated model, which equates all the expected statistics (means, variances, and covariances) to the corresponding observed statistics. The degrees of freedom for the  $\chi^2$  goodness-of-fit statistic equals that for the fitted model subtracted from that for the saturated model. When models are nested (ie, identical with the exception of constraints that involve setting specific parameters to zero), the difference in fit between models can be tested by  $\Delta \chi^2$ , using as its degrees of freedom the difference in degrees of freedom between the 2 models. If the  $\chi^2$  difference is statistically nonsignificant, the more parsimonious nested submodel is selected, as the test indicates that model fit does not deteriorate with the additional constraints.

### Directional Analyses: Examination of the Nature of the Association Between PTSD and ND

The direction of the relationships between PTSD and ND was examined using 2 different approaches. We first examined the data descriptively. Participants were divided into 6 groups based on lifetime presence or absence of trauma, PTSD, and ND. Age-at-onset data were examined for 2 of the 6 groups: (1) those with lifetime histories of trauma and ND and (2) those with lifetime histories of trauma, PTSD, and ND. Members of these 2 groups were then classified by primacy of diagnosis. This enabled us to examine the prevalence of different patterns of PTSD-ND comorbidity and to calculate ORs and 95% CIs for these patterns.

We then followed the guidelines proposed by Chilcoat and Breslau<sup>30,46</sup> for testing etiologic explanations for the relationship between PTSD and substance use disorders. Cox proportional hazards models with time-dependent covariates were used to estimate the hazards ratio, which is defined as the risk of an outcome for those with and without a specified risk factor.<sup>47</sup> Such models test whether time to an outcome (eg, ND) differs according to the status of the independent variables (eg, trauma exposure).

Time was indicated by the chronological age of the participant at the time of interview. Participants not experiencing the specific outcome by the time of the interview were censored at their current age. Temporality could not be determined if the outcome and the time-dependent covariate had onset times that occurred during the same year. Following the lead of other investigators,<sup>46</sup> observations with onsets occurring in the same year were censored 1 year earlier. Models were estimated using the XTCCO procedure in Stata.<sup>40</sup> The ages at onset of ND, MD, alcohol and drug A/D, CD, traumatic exposure, and PTSD were determined using retrospective data from the Diagnostic Interview Schedule Version III—Revised. For diagnoses, age at onset was defined as the earliest onset of symptoms for those meeting lifetime criteria for a disorder. Age at trauma exposure was defined as the retrospectively reported age at the worst traumatic event.

The direction of the relationship between ND, trauma exposure, and PTSD was examined using a series of 4 survival mod-

els: (1) trauma exposure, among those who did not develop PTSD, predicting ND onset; (2) PTSD, among those exposed to trauma, predicting ND onset; (3) ND predicting exposure (without PTSD); and (4) ND predicting PTSD onset among trauma-exposed men. All models included demographics and military service characteristics. Preexisting CD, MD, and alcohol and drug A/D were entered as time-dependent covariates. Time-dependent covariates allow the status of certain independent variables (eg, trauma exposure, PTSD, and ND) to change across time and to take into account the timing of the dependent and independent variables. Thus, observations contribute information only until the time the event occurs or the time of censoring.

## RESULTS

### PREVALENCE OF TRAUMA EXPOSURE, PTSD, AND ND

Of 3065 participants (45.4% of the sample) who reported exposure to 1 or more traumatic events, 649 (21.2%) received a lifetime diagnosis of PTSD. There were 3221 participants (47.8%) with a lifetime history of ND. The prevalence of trauma exposure and PTSD did not differ for MZ vs DZ twin pairs. The prevalence of ND was slightly lower in MZ pairs (46.2%) than in DZ pairs (49.6%). Zygosity prevalence differences were adjusted for in the analyses.

#### Is There an Association Between PTSD and ND?

The prevalence of ND was 52.0% among individuals exposed to trauma who did not develop PTSD and 71.7% among those with PTSD. These prevalences are elevated compared with that for ND among those who were not trauma exposed (40.5%). Nicotine dependence was significantly associated with trauma without PTSD (OR, 1.31; 95% CI, 1.18-1.45) and PTSD (OR, 2.34; 95% CI, 1.92-2.84) in unadjusted analyses.

#### Is the Correlation Between PTSD and ND Explained by Shared Risk Factors?

After adjusting for potential shared risk factors, including demographics, military service characteristics, and comorbid psychiatric and substance use disorders, the association between ND and trauma exposure (OR, 1.16; 95% CI, 1.04-1.31) and PTSD (OR, 1.55; 95% CI, 1.22-1.97) was attenuated but remained significant ( $P < .001$ ).

#### Is the Correlation Between PTSD and ND Explained by Shared Genetic or Common Environmental Effects?

**Table 1** provides the tetrachoric correlations for PTSD and ND by zygosity. The higher cross-twin cross-phenotype correlations in MZ twins compared with DZ twins suggested genetic effects on the PTSD-ND association.

Bivariate twin modeling was used to test whether the association between PTSD and ND in participants exposed to trauma was accounted for by shared familial vulnerability. The univariate model-fitting results for PTSD and ND in this sample have been published previously.<sup>15,18,48</sup> The best-fitting bivariate model consisted of

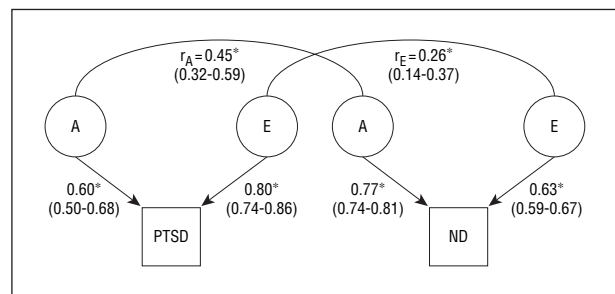
**Table 1. Tetrachoric Correlation Matrix for Posttraumatic Stress Disorder and Nicotine Dependence**

	PTSD Twin 1	ND Twin 1	PTSD Twin 2	ND Twin 2
Monozygotic (n = 1874)				
PTSD twin 1	1.00			
ND twin 1	0.34	1.00		
PTSD twin 2	0.37*	0.23†	1.00	
ND twin 2	0.20†	0.61*	0.30	1.00
Dizygotic (n = 1498)				
PTSD twin 1	1.00			
ND twin 1	0.34	1.00		
PTSD twin 2	0.14*	0.10†	1.00	
ND twin 2	0.13†	0.30*	0.34	1.00

Abbreviations: ND, nicotine dependence; PTSD, posttraumatic stress disorder.

\*Cross-twin, same-phenotype correlations.  $P < .05$  for all.

†Cross-twin, cross-phenotype correlations.  $P < .05$  for all.



**Figure 1.** Standardized parameter estimates for the bivariate model of association between posttraumatic stress disorder (PTSD) and nicotine dependence (ND) in male twins. The model presents the standardized parameter estimates of the AE model for PTSD and ND and their genetic ( $r_A$ ) and individual-specific environmental ( $r_E$ ) correlations. A and E refer to additive genetic and individual-specific environmental (including error) effects. The model is displayed for twin 1 only; the model for twin 2 would look identical. The variances of the latent variables are fixed at 1. The parameter estimates are squared to determine how much of the variation in each phenotype is accounted for by latent factors. All parameter estimates are statistically significant. Values in parentheses indicate confidence intervals; asterisks,  $P < .05$ .

significant genetic and individual-specific environment factors affecting the covariation between phenotypes. This model provided excellent fit to the data ( $\chi^2_{14} = 5.57$ ;  $P = .98$ ) (**Figure 1**).

Model fit did not deteriorate significantly if the common environmental effects specific to PTSD and ND and those affecting their covariation were fixed to zero ( $\Delta \chi^2_3 = 0.45$ ;  $P = .93$ ). However, model fit deteriorated significantly if additive genetic effects ( $\Delta \chi^2_1 = 43.28$ ;  $P < .001$ ) or individual-specific environmental effects ( $\Delta \chi^2_1 = 18.10$ ;  $P < .001$ ) were hypothesized to have no effect on the PTSD-ND association. The best estimate of the phenotypic correlation between liability to PTSD and ND was 0.34 (95% CI, 0.29-0.39). The extent to which shared genetic effect generates a correlation between the 2 phenotypes was estimated by multiplying the standardized parameter estimate for the additive genetic path for PTSD (0.60) by the additive genetic path for ND (0.77) by the genetic correlation between PTSD and ND ( $r_A = 0.45$ ), equaling 0.21. Thus, approximately 62% (0.21/0.34) of

**Table 2. Patterns of the Lifetime Relationship Between ND, Trauma, and PTSD in 6654 Members of the Vietnam Era Twin Registry\***

Diagnostic Pattern			Pattern Prevalence, No. (%)	ND Primary, No. (%)	Trauma Precedes ND, No. (%)	PTSD Precedes ND, No. (%)	Age, Mean (SD), y
ND	Trauma	PTSD					
No	No	No	2163 (32.5)	NA	NA	NA	42.2 (2.8)
Yes	No	No	1475 (22.2)	NA	NA	NA	41.8 (2.7)
No	Yes	No	1161 (17.5)	NA	NA	NA	42.1 (2.8)
Yes	Yes	No	1255 (18.8)	540 (43.0)	715 (57.0)	NA	41.7 (2.7)
No	Yes	Yes	184 (2.8)	NA	NA	NA	41.9 (2.5)
Yes	Yes	Yes	416 (6.3)	192 (46.2)	28 (6.7)	196 (47.1)	41.3 (2.7)

Abbreviations: NA, not applicable; ND, nicotine dependence; PTSD, posttraumatic stress disorder.

\*Forty-nine participants were not included because order of onset for ND and trauma/PTSD could not be determined. Forty-one participants were missing age-at-onset data and are not included in this table.

**Table 3. Unadjusted and Adjusted Relative Hazard Ratios for ND by Trauma Exposure (No PTSD) and Other Mental Disorders in 6095 Men**

Risk Factors for ND	Relative Hazard Ratio for ND (95% CI)	
	Unadjusted	Adjusted*
Trauma exposure	1.46 (1.34-1.60)†	1.49 (1.35-1.64)†
Southeast Asia service	NA	1.02 (0.94-1.11)
Less than a high school education at military entry	NA	1.31 (1.16-1.47)†
Age at entry into the military (years)	NA	0.85 (0.82-0.88)†
Pretrauma conduct disorder	NA	1.31 (1.13-1.51)†
Pretrauma major depression	NA	1.55 (1.31-1.83)†
Pretrauma alcohol abuse/dependence	NA	1.88 (1.73-2.04)†
Pretrauma drug abuse/dependence	NA	1.63 (1.41-1.87)†

Abbreviations: CI, confidence interval; NA, not applicable; ND, nicotine dependence; PTSD, posttraumatic stress disorder.

\*Estimates of hazard ratios for ND are also adjusted for zygosity, minority race, father did not graduate from high school, mother did not graduate from high school, maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, and maternal/paternal problems with the law.

† $P < .001$ .

the PTSD-ND covariance is accounted for by shared genetic effects. The remaining 38% is accounted for by individual-specific environmental effects.

### What Is the Direction of the Relationship Between Trauma/PTSD and ND?

The mean  $\pm$  SD age at onset was similar for ND (24.01  $\pm$  7.80 years) and PTSD (24.20  $\pm$  7.24 years). **Table 2** gives the prevalences for alternative patterns of association among trauma exposure, PTSD, and ND and temporal orderings within diagnostic patterns. For example, row 6 shows the prevalence of possible temporal orderings for the 6.7% of the sample that had a lifetime diagnosis of PTSD and ND. Nicotine dependence occurred before the onset of PTSD for 46.2% of those participants; PTSD occurred before the onset of ND for 47.1%. In contrast, ND occurred after a traumatic event but before the onset of PTSD for only 6.7%. Row 4 shows the prevalence of possible temporal orderings for the 18.8% of the sample exposed to trauma that

did not develop PTSD and had a lifetime diagnosis of ND; ND was primary for 43.0%.

Using data from Table 2, we calculated ORs and 95% CIs for 4 directional relationships between trauma/PTSD and ND: (1) among those without ND before trauma exposure, trauma without PTSD did not significantly predict subsequent ND (OR, 0.90; 95% CI, 0.80-1.01;  $P = .08$ ); (2) among trauma-exposed individuals without ND before PTSD, PTSD was associated with a significantly increased risk of subsequent ND (OR, 1.73; 95% CI, 1.38-2.17;  $P < .001$ ); (3) among those without trauma exposure before ND, ND did not significantly increase risk of trauma (OR, 0.94; 95% CI, 0.84-1.05;  $P = .28$ ); and (4) among those without trauma exposure before ND, ND was associated with a 2-fold increased risk of PTSD in those exposed to trauma (OR, 2.24; 95% CI, 1.78-2.83;  $P < .001$ ).

**Table 3** provides the unadjusted and adjusted hazard ratios and 95% CIs for the association between trauma and ND, and **Table 4** provides the results for PTSD. Trauma without PTSD and PTSD among trauma-exposed men were associated with an increased risk of ND. The associations between trauma/PTSD and ND remained significant, although attenuated, after adjusting for shared risk factors. The results given in **Table 5** demonstrate that the risk of trauma exposure was higher in those with preexisting ND, but the association was largely attenuated after controlling for shared risk factors. Nicotine dependence was associated with a significantly increased risk of PTSD (among veterans exposed to trauma) in unadjusted analyses. The association was not attenuated in adjusted analyses.

### COMMENT

The results of the present study support a significant, robust association between PTSD and ND among members of the VET Registry. The magnitude of association remained substantial after controlling for a wide range of potential shared risk factors not accounted for in previous research, including parental education, parental psychiatric history, military service characteristics, and preexisting CD, MD, and alcohol and drug A/D. Most of the PTSD-ND association was accounted for by shared genetic effects. However, individual-specific environmental effects accounted for 38% of the phenotypic covari-

ance, suggesting that the association is not entirely genetically mediated. Significant individual-specific environmental effects on phenotypic covariance are consistent with a PTSD-ND relationship beyond shared familial vulnerability. This relationship could be causal or could result from shared measurement error or environmental risk factors uncorrelated between siblings.

We tested 4 directional models for the relationship between PTSD and ND. Our results illustrate the complexity of PTSD-ND comorbidity. We cannot completely rule out any of the 4 models; however, the magnitude of the associations differed across models, and this may have implications for inferring causality. The strongest association in the pattern and survival analyses was consistent with the explanation that preexisting ND increases the risk of PTSD onset. In survival analyses, preexisting ND was associated with an almost 2-fold increased risk of PTSD in trauma-exposed individuals, even after adjusting for shared risk factors. Models in which preexisting trauma and PTSD were associated with risk of ND onset produced weaker associations (ORs, 0.90 and 1.73 using pattern data and 1.49 and 1.36 in adjusted survival analyses, respectively). The evidence for preexisting ND increasing risk of trauma was particularly weak; the association was not significant in the pattern analysis and was reduced almost to nonsignificance in adjusted survival analyses.

Our finding that preexisting ND is associated with significantly increased risk of PTSD requires further investigation. Nicotine dependence may convey additional risk of PTSD in exposed individuals via the effects of long-term smoking on the central nervous system. For example, there is evidence that long-term smoking produces dysregulation of the hypothalamic-pituitary-adrenal system. Evidence from animal models suggests that drugs of abuse and stress trigger similar changes in midbrain dopaminergic function.<sup>49</sup> Significant evidence suggests that long-term smoking produces a dysregulation of neural stress systems (eg, hypersecretion of cortisol).<sup>8</sup> Constituents of tobacco smoke inhibit monoamine oxidases (A and B), the enzymes involved in the breakdown of monoamines, including dopamine, serotonin, and norepinephrine,<sup>50</sup> an effect that seems to normalize after successful smoking cessation.<sup>51</sup> Indeed, long-term smoking may act to sensitize neurobiologic stress response systems.<sup>52</sup> These neurobiologic effects may lead to vulnerability to developing PTSD after trauma exposure.

Our finding of shared genetic effects on PTSD and ND may reflect a shared neurobiologic etiology for the 2 phenotypes. Evidence that the neurobiologic effects of smoking seem to be similar to those triggered by stressors is consistent with a shared etiology. Our findings also have implications for research aimed at identifying genes involved in both phenotypes. Our data suggest that some of the same genes affect variation in PTSD and ND; thus, any gene found to be associated with one phenotype may be a viable candidate for the other. Genes involved in dopaminergic pathways have been implicated in both disorders.

Our finding that PTSD is associated with increased risk of ND onset is consistent with the well-documented association between stress and smoking.<sup>52</sup> Breslau et al<sup>7</sup> also

**Table 4. Unadjusted and Adjusted Relative Hazards Ratios for ND by PTSD and Other Mental Disorders Among 2588 Trauma-Exposed Men**

Risk Factors for ND	Relative Hazard Ratio for ND (95% CI)	
	Unadjusted	Adjusted*
PTSD	1.51 (1.30-1.75)†	1.36 (1.14-1.61)†
Southeast Asia service	NA	0.74 (0.58-1.00)
Less than a high school education at military entry	NA	1.37 (1.18-1.58)†
Age at entry into the military	NA	0.86 (0.83-0.90)†
Combat exposure	NA	1.14 (1.05-1.23)‡
Pre-PTSD conduct disorder	NA	1.27 (1.10-1.47)§
Pre-PTSD major depression	NA	1.14 (0.97-1.34)
Pre-PTSD alcohol abuse/dependence	NA	1.88 (1.66-2.11)†
Pre-PTSD drug abuse/dependence	NA	1.59 (1.38-1.83)†

Abbreviations: CI, confidence interval; NA, not applicable; ND, nicotine dependence; PTSD, posttraumatic stress disorder.

\*Estimates of hazard ratios for ND are also adjusted for zygosity, minority race, father did not graduate from high school, mother did not graduate from high school, maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, and maternal/paternal problems with the law.

† $P < .001$ .

‡ $P < .05$ .

§ $P < .01$ .

**Table 5. Unadjusted and Adjusted Relative Hazard Ratios for Trauma Exposure (No PTSD) and PTSD by ND**

	Relative Hazard Ratio (95% CI)	
	For Trauma Exposure	For PTSD in Exposed
ND (unadjusted)	1.27 (1.15-1.40)*	1.89 (1.59-2.24)*
ND (adjusted)†	1.17 (1.05-1.30)‡	1.98 (1.61-2.42)*

Abbreviations: CI, confidence interval; ND, nicotine dependence; PTSD, posttraumatic stress disorder.

\* $P < .001$ .

†Estimates of hazard ratios for trauma exposure and PTSD are adjusted for zygosity, minority race, father did not graduate from high school, mother did not graduate from high school, maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, maternal/paternal problems with the law, Vietnam service, age at entry into the military, education less than high school at entry into the military, preexisting conduct disorder, major depression, and alcohol and drug abuse/dependence. Estimates of hazard ratios for PTSD are also adjusted for combat exposure.

‡ $P < .05$ .

found an increased risk of ND in individuals with PTSD. The present study controlled for a larger number of potential confounders, including MD, which is highly comorbid with PTSD and ND. Data are from a Vietnam era cohort of men who served in the military rather than young male and female adults in the general population. Tobacco use was normative in the military during the time our participants served, and our participants have almost twice the prevalence of PTSD compared with men in the general population. Despite these differences, our results provide further support for the conclusions of Breslau et al<sup>7</sup> and suggest that the findings are not entirely attributable to shared familial vulnerability.

Our findings are subject to several limitations. First, although we tested competing etiologic hypotheses, we did not prove causality. Rather, we provide evidence as to which causal models are more or less viable. Second, the sample consisted entirely of male Vietnam era veterans. The relationship between ND and PTSD may not generalize to civilians, females, or other male cohorts. Third, our assessment of ND, trauma exposure, PTSD, and their dates of onset were undertaken retrospectively. If individuals who had PTSD were more likely than those who did not to recall a history of preexisting ND or vice versa, this would inflate our associations. Fourth, we attempted to control for a wide range of shared risk factors that might have confounded the association between ND and PTSD. However, it remains possible that unaccounted for factors exist. Finally, basing our data on the *DSM-III-R* and not the *DMS-IV* criteria likely did not affect the substance of our results.<sup>53,54</sup>

In conclusion, understanding the relationship between ND and PTSD among those who serve in the military remains a particularly important public health goal. Military entry often occurs in young adulthood; young adults who are daily smokers are at high risk for ND.<sup>53</sup> Approximately 1 million men are in active duty in the US armed forces,<sup>55</sup> and this number is likely to increase. Given the recent conflicts in Iraq and Afghanistan, active-duty military personnel are at high risk for combat exposure and PTSD.<sup>56</sup> Combat exposure is one of the traumas with a high conditional risk for PTSD among men in the general population.<sup>9</sup> Thus, PTSD and ND are more likely to co-occur among active-duty military personnel and recent veterans than among civilians in the same cohort.

To inform etiology and intervention, it is important to establish underlying mechanisms for the association between ND and PTSD. Breslau et al<sup>7</sup> showed that PTSD increases the risk of onset of ND and alcohol and drug A/D. Their data and ours suggest that early PTSD treatment may prevent the onset of substance-related disorders. In addition, our data suggest that preexisting ND was associated with a 2-fold increased risk of PTSD when exposed to traumatic events such as combat. If this relationship were replicated, it would suggest that trauma-exposed individuals with a history of ND should be targeted with interventions to prevent PTSD.

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