Published in final edited form as:

Gen Hosp Psychiatry. 2006 ; 28(5): 408–413. doi:10.1016/j.genhosppsy.2006.05.007.

Is the association between posttraumatic stress disorder symptoms and poor health due to a common familial or genetic factor?

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Abstract

Objective—The objective of this study was to identify genetic, familial and environmental contributions to the association between posttraumatic stress disorder (PTSD) symptoms and poor health.

Methods—A community sample of 1852 twin pairs was assessed for symptoms of PTSD [with the Impact of Events Scale (IES)] and self-reported global health status using a single five-level question. An ordinal logistic regression model estimated odds ratio/s (OR) for the association between PTSD and health status. Within-pair analysis assessed confounding by familial and genetic factors and adjusted for the possible confounding influence of age, sex, race, education and self-reported physician diagnosis of depression.

Results—The IES was strongly and significantly associated with self-reported health [OR = 1.8; 95% confidence interval (95% CI) = 1.5–2.2; highest quartile vs. lowest quartile]. This association remained significant in within-pair analysis (OR = 1.3; 95% CI=1.0–1.7), but after further adjustment for sociodemographics and depression, it was no longer significant ($P_{\text{trend}}=.17$). Separate analysis by zygosity did not show differential effect in monozygotic or dizygotic pairs.

Conclusion—These findings suggest that the association between PTSD symptoms and poor health is, in part, due to familial confounding and sociodemographic factors. Little evidence of confounding by genetic factors was found. These findings suggest that early prevention efforts would have the greatest potential for improving poor health in PTSD-prone patients, whereas later intervention efforts directed at treating PTSD may have a more limited impact on improving poor health.

Keywords

Posttraumatic stress disorder; Poor health; Familial; Genetic; Twin

1. Introduction

Accumulating evidence suggests that posttraumatic stress disorder (PTSD) is linked to both objective and subjective indices of poorer health [1]. Studies have particularly noted a significantly greater rate of aversive physical symptoms [2,3], worse physical health status (including physical function), role limitations due to physical problems and bodily pain [3–5], a greater frequency of medical conditions and diagnoses [3,4], and a higher utilization of medical care services, resulting in greater health care costs [6]. Among anxiety disorders, only panic disorder has a comparable rate of health care use and costs [7].

A decade of work has sought to reduce the health care costs and medical morbidity associated with depression by improving its treatment [8,9]. Based on these investigations, numerous publications have cited the association between PTSD and poor health as one rationale for improving treatment in people suffering from PTSD. In particular, several authors have suggested that better treatment for PTSD could result in reduced medical morbidity and health care costs, in addition to the amelioration of PTSD symptoms and their associated functional disability [6,10,11]. Although this inference suggests that PTSD directly leads to increased physical symptoms, medical problems and health care use, evidence is based on cross-sectional data, with limited adjustments for confounding factors. In fact, some studies have shown that treating patients for their depression may be insufficient to reduce associated health care costs [12,13], suggesting that the association between depression and poor health may not be strictly causal.

PTSD and poor health could be associated for three reasons: PTSD causes poor health, poor health causes PTSD or some third factor causes both, resulting in a secondary and spurious association between the two. This study examines a sample of twins enrolled in a community-based registry in Washington State. Twin studies can assess both shared factors (using between-pairs comparisons) and individual factors (using within-pair comparisons). This provides a unique opportunity to determine whether the association between PTSD symptoms and poor health is due to some third common factor [i.e., either a genetic or a “common environmental” (familial) factor] and to explore potential genetic and environmental determinants of this association. Several previous studies have demonstrated that PTSD appears to have a familial or genetic component. For example, a family study of Cambodian refugees living in the western United States found that parental PTSD was associated with a fivefold increased risk of PTSD in their offspring [14]. Likewise, findings from a study of male veterans in the Vietnam Era Twin Registry suggest that genetic factors account for about 30% of variance in liability for most PTSD symptoms in all three symptom clusters [15] and may also mediate shared vulnerability, which contributes to the association between major depression and PTSD. Similarly, recent analyses have demonstrated distinct genetic contributions to health care need and utilization [16]. Thus, in these analyses, we address the following questions: (a) Are symptoms of PTSD and poor health associated? (b) Do genetic or common environmental (i.e., “familial”) factors account for the association between PTSD symptoms and poor health?

2. Methods

2.1. Sample

The University of Washington Twin Registry is a community-based sample of twins derived from driver's license applications at the Washington State Department of Licensing. The Department of Licensing asks every new applicant if he/she is a member of a twin pair to avoid issuing duplicate license identification numbers to twins. In September 1998, an agreement to transmit a weekly electronic list of all new driver's license applicants comprising a twin pair to the University of Washington was reached between the University of Washington and the

Department of Licensing. Upon receiving the names from the Department of Licensing, the University of Washington Twin Registry staff send each twin an invitation to join, a brief survey to complete and an incentive. If the twin does not respond, he/she is mailed a second invitation and survey. Once the index twin is enrolled, the cotwin is mailed a survey using contact information provided by the index twin. Currently, the University of Washington Twin Registry includes data for 1870 twin pairs.

2.2. Survey

The survey contains items on demographics, self-reported health symptoms, physician-diagnosed health conditions (including PTSD and depression) and abridged psychiatric measures, such as the Impact of Events Scale (IES) [17].

2.2.1. Zygosity assignment—As part of the mailed survey, all twins were asked questions about childhood similarity to assess zygosity. Studies have shown that questions about childhood similarity in twin pairs can be used to correctly classify zygosity with an accuracy of 95–98%, compared to biological indicators [18,19]. Based on these questions, a zygosity assignment algorithm, which identified 1042 monozygotic (MZ) and 828 dizygotic (DZ) pairs, was applied to all pairs.

2.2.2. Sociodemographic factors and clinical conditions—The sociodemographic factors collected included age, race, gender and education. Age was calculated from the year of birth. The twins were asked if they were White, Black, Asian/Pacific Islander, Native American, Hispanic/Latino or other. We dichotomized responses to White or other. For education, we asked about the highest level of education completed (kindergarten to graduate school). A single question also inquired about a physician diagnosis of depression.

2.2.3. PTSD symptoms—PTSD symptoms were identified using the IES, which assesses current subjective distress resulting from a stressful life event. Because of the well-known and reported reluctance of individuals with PTSD to seek evaluation and treatment [20], we did not use self-reported physician diagnoses of PTSD. The IES captures specific qualities of conscious experience that encompass stressful life events, such as bereavement or personal injuries from accidents, violence, illness or surgery [17]. PTSD is a disorder in which an overwhelming traumatic event results in intense fear, helplessness, horror and avoidance of stimuli associated with the trauma [21]. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for PTSD consist of intrusion, avoidance and hyperarousal. The IES, however, only captures the intrusion and avoidance symptom criteria. Yet, previous studies have shown that the IES is strongly correlated with a diagnosis of PTSD [22–24]. We used 11 of 15 original IES items. Based on a cluster analysis conducted by the developers of the IES, we deleted four items that had the poorest correlation with the IES intrusion and avoidance subscales [17]. We assessed the internal reliability of the IES using Cronbach's α , and we assessed its validity by examining its concordance with self-reported physician diagnosis of PTSD. For the 11 IES items used in this analysis, the Cronbach's α was .90, indicating a high degree of internal consistency. Likewise, the validity of the IES was demonstrated by a strong and significant trend between the IES and self-reported physician diagnosis of PTSD ($\chi^2_{\text{trend}}=59.3, P<.0001$).

Each item has four response categories (0=*not at all*, 1 = *rarely*, 3 = *sometimes*, 5 = *often*); these values are summed to create an overall score (range, 0–55). We grouped the scores into quartiles, representing increasing levels of current subjective distress: 0–2 (*lowest distress*), 3–16, 17–28 and 29+ (*highest distress*). In this analysis, we only included twins who answered at least 6 of 11 IES items and, as previously recommended, missing values were imputed using the respondent's average score across completed items [25]. For example, if a twin did not

answer two IES items, we used the mean score across the nine completed items to impute values for the two missing items.

2.3. Health status

A single question from the Short Form 36 was used to measure the general perception of health [26]. The question asked subjects to describe their health, choosing the terms *excellent*, *very good*, *good*, *fair* or *poor*. Responses to this question are independently associated with specific health problems, use of health services, changes in functional status, recovery from episodes of ill health and mortality [27–31]. It is thought to have particular validity when predicting help-seeking behavior and health service use [32]. A recent study has also shown that about 40% of variance in this single item, when administered to a cohort of Vietnam veterans, appears to be genetic [33]. However, because this global measure of poor health likely reflects a combination of recognized medical conditions, physical symptom complaints of unclear etiology and a propensity to seek or use health care, we cannot determine if genetic effects contribute to each of these health domains, although such effects contribute to this overall measure.

2.4. Statistical analysis

Of the 1870 pairs available for the current analysis, 18 pairs were excluded because both twins had missing data for key variables. Among the 1852 pairs included in the analyses, 1584 had complete data for both members. The remaining 268 pairs had complete data for only one member. However, the analytic techniques described below allow individual members of a pair to contribute to the analysis.

The initial descriptive analysis examined the distribution of sociodemographic factors and depression according to IES quartiles. To investigate the association between the IES and health status, a Generalized Estimating Equations model was fitted to twin data [34]. This approach is appropriate because observations between twin pairs are not statistically independent — an assumption made for classical approaches to estimation and testing. Twin data are multilevel or clustered, where twins are the cluster. These models account for lack of independence by using a sandwich estimator for variance.

We initially modeled the association between the IES and health status to estimate the overall effect in all twin pairs. A 1-*df* chi-square was used to test for a trend between continuous IES scores and the ordinal measure of health status. We also created indicator variables for quartiles of the IES, with the lowest quartile serving as the reference level to estimate odds ratio/s (OR) and 95% confidence interval/s (95% CI). Our overall model specification represents a weighted average of within-pair and between-pairs information [34]. We then refit our model to obtain separate estimates of the IES–health status association within and between pairs. In this context, within-pair effects are free from confounding due to familial factors (whether genetic or common/shared environmental), while between-pairs effects are unadjusted for familial influence. For both overall model and within/between specification, we then adjusted the IES–health status association for age, sex, race, marital status, education, body mass index and depression. In our subsequent modeling, we specified within and between effects separately for MZ and DZ pairs. Because DZ twins share only 50% of their genes, on average, a within-pair effect is adjusted for common familial factors; MZ twins have identical genes and the within-pair effect is adjusted for both common familial and genetic factors. Furthermore, these models were all adjusted for age, sex, race, marital status, education, body mass index and depression. Lastly, we statistically tested for MZ versus DZ differences in the within-pair association between IES and health status; differential effects, where the association is stronger in DZ pairs than in MZ pairs, would suggest that there is genetic mediation of the IES–health status association [35].

A simple but useful measure to assess the influence of confounding factors is the confounding risk ratio [36]; the confounding risk ratio is defined as the ratio of the unadjusted risk ratio to the adjusted risk ratio. The magnitude of the confounding risk ratio provides an indication of the strength of confounding factors in the data. A confounding risk ratio of 1 suggests that confounding factors have no effect on unadjusted association; a confounding risk ratio of either > 1 or < 1 describes the extent that confounding accounts for the unadjusted association. In the context of the analysis of twin data, the confounding risk ratio comparing the ratio of unadjusted overall OR to within-pair OR provides an indication of the extent of common environmental and/or genetic confounding.

3. Results

Table 1 describes the sample according to quartiles of IES scores. Fifty-six percent of the sample comprises MZ twins; the mean age was 34 years old and 61% of the twins were female. Most twins had some college education (57%), and the prevalence of self-reported physician diagnoses of depression was 20%. We observed an increasing trend of self-reported physician diagnoses of depression and PTSD with higher IES scores.

Table 2 presents the association between the IES and health status in all twins. A modest and significant association was noted between the IES score and health status in all twins ($P_{\text{trend}} < .01$). Compared to those in the lowest IES quartile, twins in the highest IES quartile were 1.8 times more likely to report poorer health. The association between IES and health was significant both between and within pairs ($P_{\text{trend}} < .01$), but the gradient of the effect was stronger in between-pairs analysis. There was some evidence of confounding due to common familial factors, with a confounding risk ratio of 1.4, when the OR estimates in the highest quartile were compared in overall and within-pair analyses.

Table 3 displays the overall, between-pairs and within-pair associations between the IES and health status, as adjusted for sociodemographic factors and depression. The overall and between-pairs analyses continued to be strongly significant ($P_{\text{trend}} < .01$), but the within-pair analysis was no longer significant ($P_{\text{trend}} = .17$). The OR comparing the overall analysis in the lowest and highest IES quartiles for health status was 1.5, while the comparable OR in the within-pair analysis was 1.1. The confounding risk ratio comparing these estimates was 1.4, which is the same value observed in the previous analysis that did not include adjustments for sociodemographic factors and depression.

Table 4 examines the overall, between-pairs and within-pair associations for IES scores and health status separately in MZ and DZ pairs after controlling for sociodemographic factors and depression. Overall, there is a significant trend between IES and health status in both MZ and DZ pairs ($P_{\text{trend}} < .01$). The OR for the association between IES and health status between pairs were similar in both MZ and DZ twins, although only the MZ effects were significant ($P_{\text{trend}} = .01$). In contrast, within-pair effects were not significant in either MZ or DZ pairs, and the OR were near unity in all quartiles. The confounding risk ratio comparing the OR in the highest quartile and the OR in the lowest IES quartile from overall and within-pair analyses was 1.3 in both MZ and DZ twins. There was no evidence of differential within-pair effects in MZ and DZ pairs based on a test of interaction ($P = .45$).

4. Discussion

We found that symptoms of PTSD, as measured by the IES, were strongly related to perceived general health status. Furthermore, an increasingly poor health status across quartiles of increasing IES scores was significant even after adjusting for demographic factors and depression. These results are congruent with numerous clinical studies [2–5,37]. Although

these previous investigations have confirmed the association between PTSD and multiple aspects of poor health, they were unable to adjust for genetic, common and unique environmental influences on this relationship.

This is the first study of PTSD symptoms and poor health status in a twin population. Our findings suggest that the association between PTSD and poor health is, in part, due to familial confounding and sociodemographic factors. That is, a third common factor contributes to both variables and partially accounts for their association. This familial confounding is a common environmental — not a genetic — effect. Thus, the genetic factors previously documented in the literature as contributing to PTSD and poor health are distinct and independent.

Our findings suggest that an unmeasured etiologic factor that is intrinsic to the common family environment and is related to both PTSD and poor health may exist. We have previously suggested that the relationship between increased health care use and the syndromes of depression and anxiety may be due to a common unmeasured “third factor” [38]. With respect to PTSD and its relation to poor health, childhood maltreatment accounts for many cases of chronic PTSD [39,40] and is also related to poor health [41], chronic medical illness [42] and excessive use of health care services [6]. Unfortunately, in this brief survey, we have no measure of this variable. Of course, some other unmeasured third factor that is common to the familial environment could also account for these findings. Whatever accounts for this link between PTSD and poor health, the mechanisms remain enigmatic. Some studies have suggested that acute and life-threatening medical illnesses can serve as a traumatic stressor, prompting the development of PTSD-like symptoms [43–45]. The relationship between PTSD and poor health might, therefore, be mutually maintaining where autonomic hyperactivity and increased hypothalamic–pituitary–adrenal activation of PTSD [46], or even immunologic alterations associated with PTSD [47,48], could worsen medical conditions.

This study has several limitations. First, although the IES is widely used as a measure of PTSD symptoms, it no longer represents the state-of-the-art in the measurement of PTSD symptoms. In addition, we were unable to include the complete 15-question version due to space limitations in our survey. Although the four questions deleted were those that were least correlated with their respective intrusion or avoidance subscale measure, we do not know the impact of these deletions. However, the internal consistency of the 11 questions that were retained was quite high. Second, the IES PTSD symptoms were not anchored on a specific traumatic experience; thus, the severity or impact of the traumatic experience is unclear. Finally, our measure of health status is based on a single question. This is a global indicator and likely represents the effect of recognized medical conditions and attendant impairments, the perception that one is “sick” and in need of medical attention, and the propensity to seek help and use medical care services.

In conclusion, our analysis, which is based on a large unselected sample of twins, found evidence that unmeasured familial factors account for a portion of the relationship between PTSD symptoms and health status. Previous studies of PTSD and various indices of poor health typically involved clinical samples with unknown selection biases. More studies need to examine the viability of mutual maintenance and shared vulnerability models, as well as the central nervous system mechanisms that may play a role in the link between PTSD and poor health. These investigations should use more specific measures of health, such as burden of medical illness, extent of physical impairments and use of health care services.

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Table 1

Demographic and clinical characteristics of all twins and across quartiles of the IES

Characteristic	Overall (N =3436)	IES ^a			
		Lowest quartile (n =887)	Second quartile (n =853)	Third quartile (n =844)	Highest quartile (n =852)
Demographic					
Age (mean years±S.D.)	34±15	35±16	35±15	32±14	33±13
Education (mean years±S.D.)	14±2	14±3	14±3	13±2	13±2
MZ (%)	56	55	58	54	57
Female (%)	61	52	55	67	71
White (%)	87	86	88	87	86
Clinical (%)					
Depression	20	9	14	21	37
PTSD ^b	4	1	2	4	10
Self-reported general health (%)					
Excellent	35	38	40	35	27
Very good	38	39	37	37	37
Good	21	18	18	22	27
Fair	5	4	4	5	8
Poor	1	1	1	1	2

^aLowest quartile, 0–2; second quartile, 3–16; third quartile, 17–28; highest quartile, 29–55.^bEleven twins had missing PTSD status.

Table 2
Between-pairs and within-pair associations of the IES and self-reported general health

IES ^a	Overall		Between pairs		Within pairs	
	OR	95% CI	OR	95% CI	OR	95% CI
Lowest quartile	1.0	–	1.0	–	1.0	–
Second quartile	0.9	0.8–1.1	0.9	0.7–1.2	0.9	0.8–1.2
Third quartile	1.2	1.0–1.4	1.2	0.9–1.5	1.2	0.9–1.4
Highest quartile	1.8	1.5–2.2	2.3	1.8–2.9	1.3	1.0–1.7
	$P_{\text{trend}} < .01$		$P_{\text{trend}} < .01$		$P_{\text{trend}} < .01$	
	$P_{\text{between vs. within}} = .43$					

^aLowest quartile, 0–2; second quartile, 3–16; third quartile, 17–28; highest quartile, 29–55.

Between-pairs and within-pair associations of the IES and self-reported general health as adjusted for sociodemographic factors and depression

Table 3

IES ^a	Overall		Between pairs		Within pairs	
	OR ^b	95% CI	OR	95% CI	OR	95% CI
Lowest quartile	1.0	–	1.0	–	1.0	–
Second quartile	0.9	0.8–1.1	1.0	0.7–1.2	0.9	0.7–1.2
Third quartile	1.2	1.0–1.4	1.2	1.0–1.6	1.1	0.8–1.3
Highest quartile	1.5	1.2–1.8	1.8	1.4–2.3	1.1	0.9–1.4
	$P_{\text{trend}} < .01$		$P_{\text{trend}} < .01$		$P_{\text{trend}} = .17$	
			$P_{\text{between vs. within}} = .20$			

^aLowest quartile, 0–2; second quartile, 3–16; third quartile, 17–28; highest quartile, 29–55.

^bOR adjusted for age, sex, race, education and depression.

Between-pairs and within-pair associations between the IES and self-reported general health in MZ and DZ twins as adjusted for sociodemographic factors and depression

Table 4

Zygosity	IES ^a	Overall		Between pairs		Within pairs	
		OR ^b	95% CI	OR	95% CI	OR	95% CI
MZ (n = 1923 twins)	Lowest quartile	1.0	–	1.0	–	1.0	–
	Second quartile	0.9	0.7–1.2	0.9	0.6–1.3	1.0	0.7–1.3
	Third quartile	1.1	0.8–1.4	1.1	0.7–1.7	1.0	0.7–1.4
	Highest quartile	1.5	1.2–2.0	1.8	1.2–2.7	1.2	0.8–1.7
		$P_{\text{trend}} < .01$		$P_{\text{trend}} = .02$		$P_{\text{trend}} = .41$	
$P_{\text{between vs. within}} = .25$							
DZ (n = 1513 twins)	Lowest quartile	1.0	–	1.0	–	1.0	–
	Second quartile	1.0	0.8–1.4	1.2	0.8–1.8	0.8	0.5–1.2
	Third quartile	1.2	0.9–1.6	1.4	0.9–2.1	1.0	0.7–1.4
	Highest quartile	1.4	1.1–1.9	1.8	1.2–2.8	1.1	0.7–1.6
		$P_{\text{trend}} < .01$		$P_{\text{trend}} = .20$		$P_{\text{trend}} = .20$	
$P_{\text{between vs. within}} = .81$							

^aLowest quartile, 0–2; second quartile, 3–16; third quartile, 17–28; highest quartile, 29–55.

^bOR adjusted for age, sex, race, education and depression.