

# Comorbidity Risks of a Cohort of Vietnam Veterans Diagnosed with Post-Traumatic Stress Disorder

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## Abstract

**Background:** Research has demonstrated that posttraumatic stress disorder (PTSD) is associated with increased risk of other mental diseases. Studies have also reported increased risk for cardiovascular diseases associated with PTSD.

**Purpose:** This study examined cause-specific comorbidity risks among a cohort of Vietnam veterans diagnosed with PTSD.

**Material and Methods:** Study subjects were selected from the Department of Veterans Affairs (VA) Agent Orange Registry (AOR). The AOR records diagnostic and demographic data for Vietnam veterans who come to VA for a health exam. The comorbidity of 2,874 veterans with PTSD was compared to that of 8,537 veterans not diagnosed with PTSD. Risks of comorbid diseases were assessed using adjusted odds ratios (OR)s.

**Results:** PTSD was associated with increased risk for several mental diseases including alcohol and drug dependence, adjusted (OR = 4.51; 95% C.I., 4.09, 5.00) and various depressive disorders. Compared to veterans with no diagnosis for mental diseases, those with a mental disease diagnosis, excluding PTSD, had increased risks for all cardiovascular diseases (OR=1.35; 95% C.I., 1.19, 1.52).

**Conclusion:** Mental disease in general, and to a lesser degree PTSD, are related to risk of cardiovascular disease among Vietnam veterans.

**Keywords:** veterans, posttraumatic stress disorder, cardiovascular disease, comorbidity

## Introduction

Estimates of posttraumatic stress disorder (PTSD) among Vietnam veterans include: 18.7% for a subset of Vietnam veterans, who were part of the National Vietnam Veterans Readjustment Study (NVVRS)<sup>1</sup> and 15% for Vietnam veterans included in the Vietnam Experience Study.<sup>2</sup> A 2015 follow-up of a sample of the NVVRS cohort reported a lifetime war zone prevalence of 17% for PTSD more than 40 years after the Vietnam War.<sup>3</sup> Veteran studies have reported a variety of mental diseases as being associated with PTSD. These comorbid diseases include; anxiety disorders, affective disorders, and substance abuse.<sup>2,3,4</sup> In addition to the well-established link between PTSD and other psychiatric or adjustment problems, research has identified an association between PTSD and chronic diseases.<sup>5,6</sup> Specifically, PTSD has been linked with increased risks of

cardiovascular diseases, including hypertension, digestive diseases, and musculoskeletal diseases.<sup>7,8,9</sup>

The nature of the association between PTSD and increased risk for other diseases has been assessed by several studies. Examining how PTSD might impact physical health, two review articles of previous research cite the following mechanisms through which PTSD effects physical health; 1) PTSD increases risk for other comorbid mental disorders that are themselves risk factors for poor physical health, such as comorbid depression and panic disorder; 2) those with PTSD may employ coping strategies that are in themselves risk factors for poor health, such as smoking, alcohol and drug dependency, poor diet and lack of exercise; and 3) PTSD is associated with neurobiological system changes that impact physical health.<sup>5, 10</sup> A specific example of a neurobiological change among

those diagnosed with PTSD compared to those not diagnosed with PTSD, is poorer endothelial function, which may increase risk for cardiovascular disease.

<sup>11</sup> Examining the association of cardiovascular disease risk factors and mental health diagnoses among a cohort of Iraq and Afghanistan veterans, a study reported that those with a mental health diagnosis, both including and excluding PTSD, had higher prevalence of cardiovascular risk factors than those with no mental health diagnosis. <sup>12</sup>

This current study was designed to further assess the long-term physical and mental health consequences of PTSD among a cohort of Vietnam veterans.

## Material and Methods

### Participants

The initial pool of 4,150 veterans diagnosed with PTSD and 113,808 not diagnosed with PTSD were selected from the 117,958 Vietnam veterans who received a Department of Veterans Affairs (VA) Agent Orange Registry (AOR) exam between calendar years 1982-1989. The years 1982-1989 were chosen as computerised data for AOR exams occurring post-1989 were not readily available and for years prior to 1982 diseases were not recorded using International Classification of Disease (ICD) codes. The AOR is a computer database containing diagnostic, demographic, and military service data for Vietnam veterans who have received a voluntary AOR medical examination at a VA Medical Center. The AOR was established in mid-1978 to monitor veterans' complaints and health problems that may have resulted from their exposure to herbicides used in Vietnam, including Agent Orange. However, any veteran who had active military service in Vietnam between 1962 and 1975 is eligible for the AOR. Veterans who report for an AOR exam are initially seen by a VA environmental health clinician who conducts a medical exam and screening. Based on the veteran's medical record and self-reported health history the clinician may refer the veteran to VA specialists, including a psychiatrist. Since 1982 all diagnostic data recorded on the AOR is coded using ICD-9 codes. A diagnosis of PTSD (ICD-9, 309.81) would have been assigned based on the diagnostic criteria in use at the time of the exam according to the DSM-III, DSM-III-R, or DSM-IV criteria.

To validate both the diagnosis of PTSD and absence of PTSD the 4,150 PTSD veterans and 113,808 non-PTSD comparison group veterans were first matched against VA's inpatient treatment records (PTF), 1982-2014, and outpatient treatment records (OPC). 1997-2014, PTF and OPC are computerised

files of diagnostic data for veterans who sought medical treatment at a VAMC as either an inpatient or outpatient. To be considered further as study-eligible all veterans had to have at least one record in either PTF/OPC that was on or after the date of their AOR exam. Reviewing eligible PTF/OPC records, only those PTSD subjects who also had a diagnosis of PTSD recorded in either PTF/OPC after the date of AOR exam were retained as study subjects. Veterans in the initial comparison group who were found to have a subsequent diagnosis of PTSD in either PTF/OPC post AOR exam date were excluded from further consideration as study participants. This secondary screening process yielded 3,364 PTSD veterans and 49,967 non-PTSD comparison group veterans. Next, PTSD veterans were frequency matched with non-PTSD veterans on facility where AOR exam took place. This matching by facility was an attempt to adjust for a variety of factors related to place of residence. These factors include socio-economic and environmental differences potentially found in rural vs. urban locations. It was hoped that facility matching would also adjust for any variation in quality and availability of treatment. PTSD veterans from facilities where there were an insufficient number of comparison group veterans from the same facility to satisfy a 1:3 match were excluded from the study. The final group of veterans included in this study consisted of 2,874 PTSD study subjects and 8,622 frequency matched comparison group veterans. A review of the data for the non-PTSD veterans revealed 85 individuals who had no diagnoses recorded in the PTF or OPC other than the recording the AOR exam itself. These 85 veterans were excluded from the study, resulting in a final comparison group of 8,537 veterans. The final cohort for this study included 2,874 veterans diagnosed with PTSD and 8,537 comparison group veterans with no diagnosis of PTSD recorded in VA treatment records.

### Data Sources

Demographic and military service characteristics were obtained from each veteran's AOR record. Diagnostic data was obtained from VA's PTF and OPC files, as well as from the veteran's AOR record, which includes diagnostic data obtained at the time of the AOR exam. All diagnostic data recorded during the AOR exam, or recorded in the PTF and OPC post AOR exam date were included in the study. All diagnostic data from either the AOR or PTF/OPC data files were coded using International Classification of Diseases 9<sup>th</sup> Revision (ICD-9) codes. <sup>13</sup>

Table 1. Demographic and Military Service Characteristics Among Agent Orange Registry (AOR) PTSD Cases and Controls

Demographic/ Military Service Characteristic	PTSD (Exposed) (n=2874)		PTSD (Unexposed) (n=8537)	
	#	%	#	%
<b>Age at Exam</b>				
27-36	797	27.7	1986	23.3
37-39	969	33.7	2207	25.8
40-43	824	28.7	1845	21.6
44+	284	9.9	2499	29.3
Mean age at Exam	39.0		42.0	
<b>Race</b>				
White	2205	76.7	6375	74.7
Non-White	669	23.3	2162	25.3
<b>Sex</b>				
Male	2869	99.8	8527	99.1
Female	5	0.2	10	0.1
<b>Branch</b>				
Army	1955	68.0	5625	65.9
Marines	694	24.1	1106	13.0
Navy	148	5.1	734	8.6
Air Force	75	2.6	1049	12.3
Other	2	0.1	23	0.2
<b>Date of Agent Orange Registry Exam</b>				
1982-1983	326	11.4	1229	14.3
1984-1985	1145	39.9	4595	53.7
1986-1987	601	20.9	1289	15.1
1988-1989	802	27.8	1424	16.9
<b>Number of Visits to VA for Healthcare Post AOR Exam</b>				
1-9	211	7.3	2420	28.3
10-59	393	13.7	2540	29.8
60-199	904	31.4	2441	28.6
>200	1366	47.5	1136	13.3
Mean Visits to VA for Healthcare Post AOR Exam	250.2		89.3	

Table 2. Adjusted Odds Ratios of Selected Diagnoses for Veterans With a Diagnosis of PTSD on the Agent Orange Registry

Major Diagnostic Category (ICD-9)*	OR (95% C.I.)**
Cardiovascular Diseases (390-459)	0.69 (0.59, 0.80)
Hypertension (401-405)	0.71 (0.63, 0.80)
All Vascular Diseases (440-448)	0.77 (0.68, 0.86)
Atherosclerosis (440)	0.79 (0.65, 0.96)
Depressive Disorder Single Episode (296.2)	7.32 (6.32, 8.48)
Depressive Disorder Recurrent (296.3)	11.46 (9.98, 13.16)
Dysthymic Disorder (3004)	5.87 (5.16, 6.67)
Alcohol/Drug Dependence (303-304)	4.51 (4.09, 5.00)

\*ICD-9 = International Classification Disease Codes 9th Revision

\*\*OR = adjusted odds ratio; CI = 95% confidence interval. Adjusted Odds Ratios were derived from logistic regression models (SAS® PROC LOGIST) and included the covariates; diagnosed with PTSD, Age at AOR Exam, Race, Sex, Branch of Service. Stepwise regression with an alpha level of 0.05 for entry into model was used to enter and remove a covariate from the model. Not all covariates met 0.05 criteria for entry into model for all diagnoses. For those diagnoses where PTSD did not meet 0.05 criteria to be entered into model NE (Not Entered) is recorded in the table.

## Data Analyses

Morbidity data were gathered from the date of the veteran's AOR exam through December 31, 2014. Based on earlier research, this study focused primarily on risk of cardiovascular diseases and mental diseases. Cause-specific morbidity risks associated with PTSD were assessed using adjusted Odds Ratios (ORs), and their associated 95% confidence intervals (CIs). All ORs were calculated using logistic regression models, generated by SASv.9® "PROC LOGIST"<sup>14</sup> The ORs were used to examine the nature of the association between PTSD and comorbid diseases, by comparing those diagnosed with PTSD to those not diagnosed with PTSD. To arrive at the best fit model, stepwise regression was used whereby effects, i.e. covariates, were entered into and removed from the model in such a way that each forward selection step was followed by one or more backward elimination steps. The stepwise selection process terminated if no further effect was added to the model or if the current model was identical to a previously visited model. This study required a  $p < .05$  significance level of the chi-square for a covariate to be entered into and remain in the model. Covariates assessed for each disease specific model were: diagnosed with PTSD (0 = no/1 = yes), age at time of AOR exam, race (0 = white/1 = non-white), sex (0 = female/1 = male), branch of service, and number of times seen

as either an inpatient or outpatient on/after date of AOR exam.

## Results

Table 1 has demographics and military service characteristics of both PTSD and non-PTSD veterans. Generally, veterans diagnosed with PTSD were younger than those not diagnosed with PTSD, with mean ages of 39 and 42, respectively. Both groups of veterans were similar regarding race (76.7% and 74.7% white, respectively) and sex, (99.8% and 99.1% male, respectively). A higher percentage of PTSD veterans served as ground troops, i.e. Army/Marines, than did non-PTSD veterans, 92.1% vs. 78.9%. The greatest contrast between the two groups of veterans was in the number of inpatient and outpatient visits. The mean number of inpatient and outpatient visits combined for VA healthcare throughout the follow-up period for PTSD veterans was 250.2 compared to only 89.3 for non-PTSD veterans. Forty-seven percent of PTSD veterans had 200 or more visits, compared to only 13.3% of non-PTSD veterans with 200 or more visits.

Table 2 has adjusted ORs for cause-specific morbidity of a priori interest associated with PTSD. As expected, PTSD was associated with statistically increased risks for other mental diseases including; depressive disorders single occurrence, (OR= 7.32,

Table 3. Adjusted Odds Ratios of Selected Diagnoses for Veterans By Mental Health Diagnosis for Veterans on the Agent Orange Registry

	Model 1* Mental Health Diagnosis Excluding PTSD	Model 2** PTSD With or Without Other Mental Health Diagnosis
Major Diagnostic Category (ICD-9)***	Adjusted OR (95% CI) (N=5461)	Adjusted OR (95% CI) (N=2874)
Cardiovascular Diseases (390-459)	1.35 (1.19,1.52)	NE
Prevalence,% (Mental Dx/Referent)	(85/70)	(89/70)
Hypertension (401-405)	1.25 (1.12,1.38)	NE
Prevalence,% (Mental Dx/Referent)	(72/56)	(77/56)
All Vascular Diseases (440-448)	1.60 (1.40,1.83)	1.53 (1.29,1.82)
Prevalence,% (Mental Dx/Referent)	(24/13)	(25/13)
Atherosclerosis (440)	1.66 (1.34-2.06)	1.76 (1.33,2.33)
Prevalence,% (Mental Dx/Referent)	(8/4)	(7/4)

Note. ICD-9 = International Classification Disease Codes 9th Revision; OR = adjusted odds ratio; CI = 95% confidence interval; NE = not entered. Diagnostic data compiled from AOR records and VA inpatient and outpatient records thru 2014.

\*\*Model 1 Adjusted Odds Ratios (OR)s associated with mental disease, excluding PTSD, were derived from logistic regression model (SAS® PROC LOGIST) and included the covariates; mental disease diagnosis (excluding PTSD), Age at AOR Exam, Race, Sex, Branch of Service. Stepwise regression with an alpha level of 0.05 for entry into model was used to enter and remove a covariate from the model. Model only included those with a mental disease diagnosis, excluding PTSD and those with no mental disease diagnosis (Referent). Not all covariates met 0.05 criteria for entry into model for all diagnoses. For those diagnoses where mental disease did not meet .05 criteria model NE (Not Entered) is recorded in the table. Referent group were those 3076 with no mental diagnosis.

\*\* Model 2 Adjusted Odds Ratios (OR)s associated with PTSD were derived from logistic regression model (SAS® PROC LOGIST) and included the covariates; PTSD, Age at AOR Exam, Race, Sex, Branch of Service. Stepwise regression with an alpha level of 0.05 for entry into model was used to enter and remove a covariate from the model. Model included all those diagnosed with PTSD and those with no mental disease diagnosis (Referent). Not all covariates met .05 criteria for entry into model for all diagnoses. For those diagnoses where PTSD did not meet .05 criteria NE (Not Entered) is recorded in the table. Referent group were those 3076 with no mental diagnosis.

\*\*\* ICD-9 = International Classification Disease Codes 9th Revision

95% C.I., 6.32, 8.48); depressive disorder recurrent episodes, (OR=11.46, 95% C.I., 9.98, 13.16); dysthymic disorder, (OR= 5.87, 95% C.I., 5.16, 6.67); and alcohol/drug dependence (OR= 4.51, 95% C.I., 4.09, 5.00). However, PTSD was not associated with an increased risk for any of the cardiovascular diseases examined. In fact, those with PTSD had a statistically significant decreased risk for all cardiovascular diseases, (OR= 0.69, 95% C.I., 0.59, 0.80). Those with PTSD also had decreased risk for specific cardiovascular diseases including;

hypertension, (OR=0.71, 95% C.I., 0.63, 0.80); all vascular diseases, (OR= 0.77, 95% C.I., 0.68, 0.86); and atherosclerosis, (OR=0.79, 95% C.I., 0.65, 0.96).

The role that mental diseases other than PTSD may have in assessing whether PTSD is associated with risk of cardiovascular disease is examined in Table 3. Model 1 assesses the risk of cardiovascular diseases among veterans with mental disease diagnoses, excluding PTSD, compared to veterans with no mental disease diagnosis. Model 2 assesses the



risk of cardiovascular diseases among all veterans diagnosed with PTSD relative to that of veterans with no mental disease diagnosis. Compared to those with no mental disease diagnosis, veterans with mental diseases other than PTSD had statistically significant increased risk for all cardiovascular diseases, (OR=1.35, 95% C.I., 1.19, 1.52); hypertension, (OR=1.25, 95% C.I., 1.12, 1.38); all vascular diseases, (OR =1.60, 95% C.I., 1.40, 1.83); and atherosclerosis, (OR=1.66, 95% C.I., 1.34, 2.06). Compared to veterans with no mental disease diagnosis, those diagnosed with PTSD did not have an increased risk of all cardiovascular diseases or hypertension (Model 2); however, there were increased risks of all vascular diseases, (OR=1.53, 95% C.I., 1.29, 1.82) and atherosclerosis, (OR=1.76, 95% C.I., 1.32, 2.33).

## Discussion

As reported in other studies, PTSD among Vietnam veterans on the AOR is associated with an increased risk for other mental disorders.<sup>2,3,4</sup> Unlike other studies<sup>7,8,9</sup>, this study did not find an increased risk of cardiovascular diseases among those diagnosed with PTSD. In fact, those with PTSD had statistically decreased risks for all cardiovascular diseases; including hypertension, all vascular diseases, and atherosclerosis when compared to veterans with no diagnosis of PTSD. A potential explanation for the decreased risk of cardiovascular diseases among those diagnosed with PTSD, may be related to the presence of mental diseases other than PTSD among the comparison group veterans. Non-PTSD veterans were selected only on the basis of not having a diagnosis of PTSD, veterans were not excluded from the potential comparison group if they had mental diseases other than PTSD. Among non-PTSD veterans in this study, 64% had a diagnosis for mental disease. While two of the previous studies reporting an association between PTSD and cardiovascular disease did not adjust for effects of potential confounding by mental diseases other than PTSD,<sup>7,8</sup> the third study adjusted for depression and the association between PTSD and risk of cardiovascular disease persisted.<sup>9</sup> In addition, two meta-analytic reviews of studies examining risk of coronary heart diseases specifically, rather than cardiovascular disease in general, also concluded that independent of depression, PTSD was associated with an increased risk of coronary heart disease.<sup>15,16</sup>

As studies have shown that mental disease, primarily depression, is related to risk of cardiovascular disease,<sup>17,18</sup> this study's comparison group may have also been at risk for cardiovascular diseases, which in turn may have diminished any detectable

risk among this study of PTSD veterans, when they were compared to non-PTSD veterans. To address what effects if any the presence of mental diseases among controls may have had on the results reported in Table 2, additional analyses were conducted to adjust for the effects of mental diseases other than PTSD. The findings presented in Table 3 appear to support the contention that Table 2 findings were due to mental diseases among the original group of comparison veterans. This finding also suggests that mental health in general, and to a lesser extent PTSD specifically, are both related to risk of cardiovascular diseases. However, mental diseases other than PTSD may be better predictors of cardiovascular disease. The lack of an association between PTSD and risk of cardiovascular diseases might also be due to exposure to trauma by both those diagnosed with PTSD and those not diagnosed with PTSD. Findings from the "Heart and Soul Study" reported that exposure to psychological trauma was associated with an increased risk of recurrent cardiovascular events and mortality, independent of psychiatric comorbidities, including PTSD and depression.<sup>19</sup> As all those in this study served in Vietnam, both PTSD and non-PTSD veterans may have been exposed to trauma and therefore their risks for cardiovascular disease would have been similar.

This study's primary limitation is the reliance on veterans from the AOR. The AOR is a self-selected cohort, and may not be representative of all Vietnam veterans with PTSD. If PTSD veterans are more likely than non-PTSD veterans to use VA for healthcare, reliance on VA treatment data may under-report diagnostic data for non-PTSD veterans. However, it is hoped that by including the number of times seen by VA as a covariate in the regression model, the effects of lower utilisation of VA healthcare by non-PTSD veterans may be minimised. This study also did not examine diagnostic data for veterans that preceded their diagnosis of PTSD. However, this study did not attempt to establish causation between PTSD and other diagnoses. Instead, the stated purpose was to examine the risk of co-morbid diseases. Finally, this study also did not assess the relative importance of specific mental diseases other than PTSD on the risk of cardiovascular diseases. Instead it adjusted for the effects of all other mental diseases in general, rather than individual diagnoses.

The findings reported here provide additional insight into the nature of the relationship between PTSD and other mental diseases on physical health comorbidities in a cohort of Vietnam veterans. The associations between cardiovascular outcomes and PTSD or other mental health diagnoses in the Vietnam cohort require careful consideration, as

previous research has demonstrated the biological plausibility of exposure to Agent Orange and the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) functioning as a contributor to cardiovascular morbidity.<sup>20</sup> Research on cellular pathways associated with development of cardiometabolic dysfunction and cardiovascular or other disease endpoints provides increasing evidence about the complex web of physiological responses to stress and trauma. Research in veterans who served after Vietnam, and non-military populations, that is focused on the natural history of disease through examination of cellular and physiological responses may provide increased tools for recognising vulnerability to disease and targets for assessing efficacy of treatment.

The increasing evidence that mental diagnoses, especially depression, is an important risk factor for cardiovascular disease outcomes suggests that early and regular screening and intervention for risk reduction is important. Regardless whether patients are in a mental health or primary care setting, consistent reinforcement of the importance of risk reduction strategies aimed at improving physical and mental health should be delivered in tandem.

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