Posttraumatic Stress Disorder and Incidence of Coronary Heart Disease: A Twin Study

Running Title: Posttraumatic Stress Disorder and CHD

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Key Words: Cardiovascular diseases; epidemiology; risk factors; stress

ABSTRACT

Objectives: To determine whether posttraumatic stress disorder (PTSD) is associated with coronary heart disease (CHD) using a prospective twin study design and objective measures of CHD.

Background: It has long been hypothesized that PTSD increases the risk of CHD but empirical evidence using objective measures is limited.

Methods: We conducted a prospective study of middle-aged male twins from the Vietnam Era Twin Registry. Among twin pairs without self-reported CHD at baseline, we selected pairs discordant for a lifetime history of PTSD, pairs discordant for a lifetime history of major depression, and pairs without either condition. All underwent a clinic visit after a median follow-up of 13 years. Outcomes included clinical events (myocardial infarction, other hospitalizations for CHD and coronary revascularization) and quantitative measures of myocardial perfusion by [N13] positron emission tomography, including a stress total severity score (STSS) and coronary flow reserve (CFR).

Results: A total of 562 twins (281 pairs) were included with mean age of 42.6 yrs at baseline. The incidence of CHD was more than double in twins with PTSD (22.6%) than those without PTSD (8.9%; $p<0.001$). The association remained robust after adjusting for lifestyle factors, other CHD risk factors and major depression (OR=2.2, 95% confidence interval, 1.2-4.1). STSS was significantly higher (+ 95%, $p=0.001$) and CFR lower (-0.21, $p=0.02$) in twins with PTSD than those without, denoting worse myocardial perfusion. Associations were only mildly attenuated within 117 twin pairs discordant for PTSD.

Conclusions: Among Vietnam era veterans, PTSD is a risk factor for CHD.

Key Words: cardiovascular diseases, risk factors, epidemiology, stress

Abbreviation List

CHD = Coronary Heart Disease

CFR = Coronary Flow Reserve

DIS = Diagnostic Interview Schedule

MI = Myocardial Infarction

PET = Positron Emission Tomography

PTSD = Posttraumatic Stress Disorder

STSS = Stress Total Severity Score

INTRODUCTION

Posttraumatic Stress Disorder (PTSD) is a psychiatric condition characterized by a persistent maladaptive reaction to the exposure to severe psychological stress (1). In the general population PTSD has a lifetime prevalence of 10-12% in women and 5-6% in men (2). A group especially affected by PTSD is military personnel exposed to combat. Among veterans serving in Southeast Asia during the Vietnam War, the lifetime prevalence of PTSD is 15 to 19%, and many continue to suffer from PTSD decades after the war (3). PTSD is even more prevalent in service members from the recent Iraq and Afghanistan conflicts (4).

A characteristic of PTSD is enhanced sympathetic nervous system reponse with trauma-reminiscent stimuli coupled with chronic dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (5). These biological perturbations could affect the cardiovascular system. Indeed, a wealth of studies has documented many physical health problems in PTSD, especially cardiovascular symptoms (6). However, a major limitation of many studies is a cross-sectional design, which limits the ability to demonstrate a temporal relationship between PTSD and coronary heart disease (CHD). The few longitudinal studies have examined PTSD symptoms rather than a PTSD diagnosis (7,8), or have relied on death certificate codes (7,9,10) or administrative records (11-13) for outcome definition. Most studies were also based on self-reported symptoms of CHD rather than objective measures (7,14-19). Finally, not all studies have found an increased cardiovascular risk with PTSD (14,17,20) or military trauma exposure (21-23). As a result, the long-term effects of PTSD on CHD risk remain unclear.

The main objective of this study is to clarify the relationship between PTSD and CHD using a prospective co-twin study design and objective measures of CHD by clinical history and positron emission tomography (PET) myocardial perfusion imaging.

METHODS

Subjects

The Vietnam Era Twin (VET) Registry is a national sample of male monozygotic and dizygotic twins from all military branches who served on active duty during the Vietnam era (1964-1975). The methods of construction have been described in detail (24). The present study is based on a follow-up of subgroups of VET Registry twin pairs selected based on their PTSD and major depression status as part of the Emory Twin Studies (25,26). We selected twin pairs born between 1946 and 1956 where at least one member had PTSD or depression, and twin pairs with both members free of PTSD and depression. We excluded pairs where at least one member reported a previous history of cardiovascular diseases, and those with contraindications to positron emission tomography (PET) with adenosine stress as previously described (25). Zygosity was obtained by DNA typing.

Baseline Assessments

Demographics and Other Baseline Factors. Data on demographics and military service were obtained from military records. Detailed sociodemographic information, combat exposure, previous history of CHD, CHD risk factors and medications, were obtained through a series of registry-wide surveys conducted between 1987 and 1992 (24,27).

Assessment of PTSD and Other Psychiatric Diagnoses. Our primary measure of PTSD was PTSD diagnosis based on the Diagnostic Interview Schedule (DIS) for psychiatric disorders according to DSM-III-R criteria which was administerd in 1992. Surveys were conducted using trained interviewers and a computer-assisted telephone version of the DIS. For 19 twins a DIS PTSD diagnosis was missing, and it was imputed based on a calculated Mississippi scale score of 80 or above (28). A 15-item PTSD-symptom scale according to the DSM-III-R diagnostic

criteria was also obtained in 1987. This scale has high internal consistency and acceptable reliability (27). A 2010-2011 VET Registry survey found a high correlation (r = 0.90) between the 15-item PTSD symptom scale and the more contemporary 17-item PTSD Checklist based on DSM-IV (unpublished data). The 1992 DIS allowed assessment of other psychiatric diagnoses including major depression and alcohol and drug abuse and dependence.

Follow-Up Assessments

After a median follow-up of 13 years, between 2002 and 2010, the selected twin pairs received an in-person clinic visit including a detailed medical history, physical exam and review of current medications by a research nurse or physician assistant. Anthropometric measurements, blood samples and behavioral questionnaires for measurement of CHD risk factors were obtained (25,26). All assessments were done blindly with respect to PTSD status.

Incidence of Cardiovascular Diseases. Symptomatic CHD was defined as having had a prior myocardial infarction or any other overnight hospitalization for CHD, based on typical signs and symptoms of acute coronary syndromes (unstable angina or acute myocardial infarction), or having undergone coronary revascularization procedures (coronary bypass surgery or percutaneous coronary angioplasty). We also collected information on cerebrovascular accidents (CVA), including strokes and transient ischemic attacks.

Myocardial Perfusion Measurements. Twins underwent myocardial perfusion imaging with PET [^{13}N] ammonia at rest and following pharmacologic (adenosine) stress during a single imaging session as previously described (25). All twins were admitted overnight in the research facility on the day prior to the PET scan. They were instructed to abstain from smoking, from drinking alcoholic or caffeinated beverages and all medications were held the morning of the PET scan.

Myocardial perfusion was quantified by means of the Emory Cardiac Toolbox, a computer technique providing objective (operator-independent) quantitative assessment of perfusion with established validity and reproducibility (29). Briefly, the three-dimensional tracer uptake distribution in the left ventricular chamber is synthetized onto a two-dimensional polar map. A stress total severity score (STSS) is computed according to published methodology (30). Moreover, we examined the percentage of subjects with an STSS of 100 or greater, which is associated with approximately a 10% decrease in event-free survival at 2 years in patients with established coronary artery disease (31).

We also performed myocardial blood flow (MBF) quantitation for the assessment of coronary flow reserve (CFR), an index of coronary vasodilator capacity that is a useful measure of coronary microvascular function (32). To calculate CFR, measurements of MBF at rest and during adenosine hyperemia were obtained as previously described (25). Our main outcome was the overall measure of CFR for the entire myocardium (across all 20 regions), defined as the ratio of maximum flow during stress to flow at rest. We also examined abnormal CFR, defined as a CFR<2.0, which has prognostic significance (33). This research was approved by the Emory Institutional Review Board, and all twins signed an informed consent.

Statistical Analysis

SAS software version 9.2 (SAS Institute) was used for statistical analysis. To assess possible response bias, we compared baseline characteristics between eligible twins who did or did not participate in our study. We also examined whether mortality differed according to PTSD over the follow-up in participants compared with nonparticipants. We used generalized estimating equation (GEE) models for categorical variables (such as incidence of CHD) and mixed effects models for continuous variables (such as STSS and CFR) with a random intercept for each pair (34). Because STSS was not normally distributed, it was log transformed; results are presented

as geometric means and percent differences. We fitted a series of sequential models that adjusted for the following a-priori chosen baseline factors: 1) socio-demographics (age, education, income); 2) service in Southeast Asia; 3) lifestyle and CHD risk factors (smoking, alcohol consumption, physical activity, hypertension); 4) major depression and 5) alcohol and drug abuse or dependence. Each model retained all variables in previous models. The interaction between PTSD and major depression was tested, and CHD risk factors at follow-up were also examined. For the CFR analysis, we further adjusted for perfusion abnormalities (STSS score). Analyses were repeated for a 3-level classification of PTSD including a "subthreshold" category, defined as meeting both the A (exposure to traumatic stress) and B (re-experiencing) criteria for PTSD, and either the C (avoidance and numbing) or D (increased arousal) criteria. Analyses were further repeated for quartiles of the PTSD symptom scale score.

Next, we compared twins discordant for PTSD. The within-pair effects are inherently controlled for demographic, shared familial and early environmental influences; in addition, daily activities and other environmental factors during the examination day were controlled by design since twin pairs were examined together. Monozygotic pairs share 100% of their genetic material in addition to early environment, thus any association within monozygotic pairs cannot be ascribed to genes or early shared environment. Dizygotic twin pairs share familial factors, but on average only share 50% of their genetic material. Therefore, comparison of the effect size between the individual-level analysis and the discordant-pair analysis of monozygotic and dizygotic twins provides information on whether genetic or other familial or shared environmental confounding is present (35).

RESULTS

Sample

Overall, 307 twin pairs were recruited and tested between 2002 and 2010. The response rate was similar in the PTSD-discordant twin pairs (127/318 twin pairs, 40%), in the depression-discordant twin pairs (93/201 twin pairs, 46%) and the control pairs (87/229 twin pairs, 38%). There were no differences in demographic characteristics, military variables, and CHD risk factors between participant and non-participant twins. There was also no evidence of differential mortality in participants and nonparticipants. In the approximately 10 years between PTSD assessment in 1992 and the start of recruitment in our study in 2002, there were only 43 otherwise eligible twin pairs where one or both twins had died, and deaths were not associated with PTSD (3.1% vs 2.3%, p=0.31). Over the entire period between 1992 and 2009 (the last year that mortality was updated in the VET Registry through death certificates), PTSD tended to be associated with total and cardiovascular mortality, but the association was similar in participants and non-participants. Among participants, the relative risk comparing those with and without PTSD was 1.8 (p=0.19) for total mortality and 1.6 (p=0.55) for CVD mortality; among nonparticipants, corresponding relative risks were 1.8 (p=0.001) and 1.8 (p=0.10).

After eliminating the second visit of 26 twin pairs with repeated assessments, our sample included 562 twins or 281 twin pairs (170 monozygotic and 111 dizygotic pairs). Of these, 137 individuals met criteria for PTSD at baseline, and 117 twin pairs (77 monozygotic and 40 dizygotic) were discordant for PTSD. Approximately half of the sample served in Southeast Asia. Twins with PTSD were more likely to smoke, to drink alcohol and to have a history of hypertension, but there were no differences in other risk factors such as BMI and diabetes (**Table 1**). A diagnosis of major depression, of alcohol and drug abuse were also higher in twins with PTSD.

Incidence of Cardiovascular Diseases

In total, 69 twins developed CHD during follow-up. As shown in **Figure 1**, the incidence of CHD was more than double in twins with PTSD (22.6%) than those without PTSD (8.9%). This difference held for each of the subcategories of acute myocardial infarction (n=31), other hospitalizations for CHD (n=20) and revascularization procedures (n=39) (all $p<0.05$). The association between PTSD and incidence of CHD remained robust after adjusting for socio-demographic factors, service in Southeast Asia, lifestyle and other CHD risk factors, major depression, and other psychiatric diagnoses (**Table 2**). In the fully adjusted model, the odds ratio was 2.1 (95% confidence interval, 1.1-3.9).

Only 18 twins reported CVA events during follow-up. These events were about twice more common in twins with PTSD (5.1%) than those without PTSD (2.5%), but the difference did not reach statistical significance ($p=0.14$).

PET Myocardial Perfusion Imaging

PET myocardial perfusion data and CFR could not be obtained in some twins. Overall, 479 twins (116 with PTSD) were included in the STSS analysis, and 416 (92 with PTSD) were included in the CFR analysis.

The STSS score was 95% higher in twins with PTSD than those without ($p=0.001$), denoting more perfusion defects (**Table 3**). A STSS of at least 100 was present in 59.5% of twins with PTSD vs 38.6% of twins without PTSD (OR=2.0, 95% CI 1.3-3.1, $p=0.001$). Extent of hypoperfusion expressed as percent of the left ventricle affected was also significantly higher in twins with PTSD that those without ($p=0.001$). Forty-two percent of twins with PTSD had an extent of hypoperfusion >10% of left ventricular mass, vs. 26% of twins without PTSD (OR=1.9, 95% CI, 1.2-2.8, $p=0.003$). Multivariable analysis did not substantially affect the relationship between STSS and PTSD (**Table 3**).

Overall, CFR was significantly lower in twins with PTSD than those without PTSD (absolute difference -0.21, p=0.02) (**Table 4**). The reduction in CFR was primarily due to lower myocardial blood flow during pharmacological stress in twins with PTSD than those without (148 vs 160 ml/min/g, p=0.01), while myocardial blood flow at rest was not different (67.8 vs 66.6 ml/min/g, p=0.46). Adjustment for sociodemographic factors and service in Southeast Asia did not substantially alter the results, but further adjustment for lifestyle factors weakened the association. Adjustment for STSS did not materially alter the difference in CFR due to PTSD (2.29 vs 2.51, absolute difference -0.22), suggesting that the microvascular circulation was involved. An abnormal CFR, defined as <2.0, was also more frequent among twins with PTSD (43.5%) than those without (24.7%, p<0.001).

Within-Pair Analyses

As shown in **Table 5**, the odds of CHD were 90% higher in twins with PTSD than their brothers without PTSD (22.2% vs. 12.8%, p=0.04). Additionally, twins with PTSD had a STSS that was 72% higher (p=0.02) and a CFR that was 0.22 points lower (p=0.03) when compared with their brothers without PTSD. Adjusting for service in Southeast Asia, lifestyle and CHD risk factors and other psychiatric diagnoses did not diminish the association for CHD incidence and STSS, although the association for CFR was attenuated and no longer significant. Results were similar in monozygotic and dizygotic twin pairs.

Additional Analyses

The interaction between PTSD and major depression was tested for all CHD outcomes and found not to be statistically significant. When analyses were repeated after excluding the 19 twins with missing PTSD DIS diagnosis who had their PTSD imputed based on PTSD symptoms, results were virtually identical. Specifically, among twins with complete PTSD DIS diagnosis, the incidence of CHD was 22.2% in twins with PTSD and 8.6% in those without

PTSD (odds ratio 3.1, p<0.001); STSS score values were 59.3 and 30.8 (p=0.002); and CFR values were 2.33 and 2.51 (p=0.04), respectively.

When analyses were conducted according to a 3-level classification of PTSD including no PTSD (n=210), subthreshold PTSD (n=207), and PTSD (n=126), only PTSD, and not subthreshold PTSD, was associated with a higher CHD risk compared with the group without PTSD (**Figure 2**). However, when analyses were conducted using quartiles of the PTSD symptom scale score, a graded association of increasing CHD risk with increasing PTSD symptom quartiles was found for both CHD diagnosis and STSS (**Figure 3**). For CHD incidence, but not for STSS, adjustment for service in Southeast Asia, lifestyle and CHD risk factors diminished this trend; additional adjustment for other psychiatric diagnoses further reduced the OR of CHD for the 4th quartile of PTSD.

At the end of the follow-up period, twins with PTSD at baseline continued to show adverse lifestyle behaviors such as current smoking (37.2% vs 21.6%), alcohol drinking (a mean of 6.4 vs 4.6 drinks/day) and sedentary behavior (Baecke physical activity score 6.9 vs 7.3). However, there were no differences in other traditional CHD risk factors such as blood pressure, history of hypertension, history of diabetes mellitus and BMI. LDL-cholesterol was significantly lower in twins with PTSD (116.6 mg/dL) than those without PTSD (122.3 mg/dL). There were also no differences in the use of cardiovascular medications including beta-blockers, statins and aspirin.

DISCUSSION

In this study of middle-aged Vietnam era Veteran twins, we found that PTSD was associated with greater than twice the risk of CHD over a median follow-up of 13 years. This association held for a clinical diagnosis of CHD as well as for objective quantitative measures of myocardial perfusion using cardiac PET. Except for CFR, the associations remained robust after adjusting

for CHD risk factors at baseline, and were independent of major depression. Additionally, the estimates were only modestly reduced when comparing twins discordant for PTSD, who are matched for sociodemographic, esrly environment and, in the monozygotic twins, genetic factors.

Our study is the first investigation linking PTSD to CHD using objective measures of myocardial perfusion in addition to a clinical diagnosis of CHD. Utilizing a co-twin design and both clinical and imaging endpoints, our study clarifies inconsistent results in previous research. The co-twin design also controls for unmeasured genetic and familial confounders that could be shared between PTSD and cardiovascular diseases.

The mechanisms underlying the link of PTSD to CHD have yet to be clarified, but alterations in the central and autonomic nervous system and neuroendocrine dysregulation are thought to play a role (1,5). Individuals with PTSD exhibit higher catecholamine levels and higher heart rate and other physiological parameters compared with controls particularly after exposure to traumatic reminders such as sound of gunfire and combat slides (1,36). Repeated sympathetic system responses to trauma reminders could lead to hemodynamic hyperactivity during everyday life which may eventually affect cardiovascular health. It could.also affect myocardial electrical stability and the risk for cardiac arrhythmias (37), and could contribute to reduced heart rate variability and baroreflex function, important risk factors for cardiac events (38). Although chronic perturbations in the HPA axis could theoretically increase CHD risk by enhancing metabolic risk factors, we found little evidence of this in our data. There was no association between PTSD and metabolic risk factors at baseline, except for a higher rate of self-reported hypertension. Notably, PTSD was also unrelated to measured metabolic risk factors at follow-up.

PTSD may also influence CHD risk through lifestyle factors. As expected, adverse lifestyle behaviors were more common in twins with PTSD than those without PTSD. However, adjusting for these factors generally accounted for a small portion of the relationship between PTSD and CHD outcomes except CFR. The impact on CFR may reflect the established effect of cardiovascular risk factors, particularly smoking, on coronary vasodilator capacity even in the short-term and in the absence of obstructive coronary stenosis (32).

When comparing twins discordant for PTSD the associations persisted, although the estimates were slightly reduced. This indicates that, to some extent, the relationship is due to familial influences or other early environmental confounding factors shared by the twins. However, even within pairs, twins with PTSD showed a higher incidence of CHD, a more compromised myocardial perfusion and a lower CFR, compared with their brothers without PTSD. Thus, the basis of the association between PTSD and CHD does not involve confounding by familial and other shared environmental factors.

The differences in imaging endpoints based on PTSD in this study are clinically meaningful. Extent and severity of myocardial hypoperfusion using operator-independent measures carries substantial prognostic value both in persons with and without coronary artery disease (31). Compared with twins without PTSD, those with PTSD had twice the odds of a STSS of 100 or greater, which is associated with approximately a 10% decrease in event-free survival in cardiac patients (31). They also had 90% higher odds of hypoperfusion affecting more than 10% of the left ventricle. Coronary flow reserve was significantly reduced, and a clinically abnormal CFR (<2.0) was 80% more common in twins with PTSD than those without.

Our study required participants to travel for an in-person examination and our participation rate was modest. It is possible that twins who elected to participate were systematically different from those who did not. However, responders and non-responders were

quite similar in their distribution of risk factors, an therefore bias due to non-response is unlikely. In addition, our within-pair results of PTSD-discordant twin pairs are free of this potential bias, since both twins participated. The use of the DIS in assessing PTSD has limitations, as all semi-structured instruments. According to a reanalysis of PTSD in Vietnam veterans, however, the DIS produces estimates of PTSD prevalence that are similar to other instruments (39). We had no access to participants' medical records to validate clinical endpoints, as this information is not routinely collected by the VET Registry. However, clinical endpoints were assessed at the in-person examination by clinical personnel. Misclassification of CHD events is low when self-reported history is compared with medical record review (40). It is anticipated that such misclassification is even lower when information is collected by clinicians during health examinations rather than by self-report. Indeed, data gathered during health examinations has often been used as gold standard (41,42). An additional limitation is that we did not have PET data at baseline. Nonetheless, our PET results corroborate the CHD incidence results. Our sample was all male and predominantly non-Hispanic white; therefore, our findings should be generalized with caution to other demographic groups. On the other hand, our study has the advantage of a prospective design and objective measures of CHD using cardiac imaging. In addition, the twin sample offers the unique advantage of controlling for potentially unmeasured confounding familial factors that may affect both the risk of PTSD and the risk of CHD.

In conclusion, among Vietnam era veterans PTSD is associated with increased risk of CHD confirmed with quantitative measures of coronary perfusion and myocardial blood flow. This increased risk is not due to a higher rate of established CHD risk factors. It is also not explained away by adverse health behaviors such as smoking and alcohol use, nor is it explained by familial risk factors shared by PTSD and CHD. Future studies should address mechanisms underlying the increased cardiovascular risk in persons with PTSD, as this

information will help guide effective prevention and treatment strategies aimed at reducing cardiovascular morbidity and mortality in persons with PTSD.

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Figure Legends

Figure 1. Incidence of CHD based on PTSD status at baseline. CHD: coronary heart disease; MI: myocardial infarction; PTSD: posttraumatic stress disorder.

Figure 2. Relationship between a 3-level classification of PTSD at baseline (no PTSD, subthreshold, and PTSD) and CHD outcomes. "Adjusted1": model adjusted for socio-demographic, lifestyle and CHD risk factors and service in Southeast Asia. "Adjusted2": Also adjusted for lifetime history of major depression and lifetime history of alcohol or drug abuse/dependence. Socio-demographic, lifestyle and CHD risk factors included in these models are the same as those listed in tables 2 through 4.

CHD: coronary heart disease; CFR: coronary flow reserve; OR: odds ratio; PTSD: posttraumatic stress disorder; STSS: stress total severity score.

* $p<0.01$ compared with no PTSD
† $p<0.01$ compared with subthreshold.
‡ $p<0.05$ compared with no PTSD.
§ $p<0.05$ compared with subthreshold.

Figure 3. Relationship between quartiles of the PTSD symptom scale score and CHD outcomes. "Adjusted1": model adjusted for socio-demographic, lifestyle and CHD risk factors and service in Southeast Asia. "Adjusted2": Also adjusted for lifetime history of major depression and lifetime history of alcohol or drug abuse/dependence. Socio-demographic, lifestyle and CHD risk factors included in these models are the same as those listed in tables 2 through 4. P values shown are for trend.

CHD: coronary heart disease; CFR: coronary flow reserve; OR: odds ratio; PTSD: posttraumatic stress disorder; STSS: stress total severity score.

Table 1. Socio-demographic, Military Service, Lifestyle, and Cardiovascular Disease Risk Factors at Military Enlistment or at Baseline (1992), by PTSD Status.

	No PTSD N =425	PTSD N =137
Socio-demographic Factors		
Age, yrs, mean (SD)	42.7 (2.4)	42.5 (2.4)
Non-white	4.0	2.2
Married at Enlistment	6.4	3.7
Education at Enlistment		
Total school years, mean (SD)	12.4 (1.3)	11.8 (1.1)
Less than High School Graduate	11.6	20.6
High School Graduate	63.4	66.2
More than High School	25.1	13.2
Family Income Category, mean (score 0-10)*	7.3 (2.2)	6.5 (2.5)
Military Service		
Branch of Service		
Army	16.2	14.6
Navy	51.1	54.0
Air Force	9.4	11.0
Marines	23.3	20.4
Enlistment year		
<1968	24.2	24.8
1968-1969	37.4	43.8
≥1970	38.4	31.4
Service in Southeast Asia	40.0	63.5

Table 1 (Continued)	No PTSD	PTSD
Lifestyle		
Cigarette Smoking		
Never	34.8	19.7
Current	30.7	51.8
Former	34.5	28.5
Physical Activity		
Not Active	11.1	8.0
Moderate Activity	60.7	64.2
Vigorous Activity	28.2	27.7
Number of Alcoholic Beverages Consumed in Typical Day, mean (SD)	0.7 (1.3)	1.2 (1.8)
Cardiovascular Risk Factors and Medications		
BMI, mean (SD)	25.8 (3.2)	25.8 (3.2)
Hypertension	15.8	25.9
Diabetes	1.2	0.7
Taking blood pressure medications	4.5	2.2
Taking daily aspirin	3.8	3.6
Other Psychiatric Diagnoses (Lifetime†)		
Major Depression	19.2	38.3
Alcohol Abuse (with or without dependence)	58.3	74.8
Drug Abuse (with or without dependence)	15.4	34.9

All data are percentages of subjects unless otherwise indicated.

* Income included total, combined family income over the previous 12 months. Categories were as follows: 1=Less than $5,000; 2=$5,000-$9,999; 3=$10,000-$14,999; 4=$15,000-$19,999; 5=$20,000-$24,999; 6=$25,000-$29,999; 7=$30,000-$34,999; 8=$35,000-$39,999; 9=$40,000-$49,999; 10=$50,000 or more.

† Lifetime is defined as having history of a disorder at any point in life.

Table 2. Multivariable analysis of the relationship between PTSD and incidence of coronary heart disease.

Model	Odds Ratio (PTSD vs. No PTSD)	95% CI	P
Unadjusted	3.0	1.7 – 5.1	<0.001
Adjusted for socio-demographic factors*	2.5	1.5 – 4.4	<0.001
+ service in Southeast Asia	2.8	1.6 – 4.8	<0.001
+ lifestyle and CHD risk factors†	2.3	1.3 – 4.2	0.006
+ major depression	2.2	1.2 – 4.1	0.01
+ other psychiatric diagnoses‡	2.1	1.1 – 3.9	0.02

CHD: coronary heart disease; CI: confidence interval; OR: odds ratio; PTSD: posttraumatic stress disorder.

*Age, education, family income

†Number of alcoholic drinks per day, smoking (never, past, current), physical activity (not active, moderate activity, vigorous activity), history of hypertension

‡ Alcohol or drug abuse/dependence

Table 3. Multivariable analysis of the relationship between PTSD and STSS in the overall sample.

	No PTSD (N=363)		PTSD (N=116)			
Model	**Geometric Mean**	**95% CI**	**Geometric Mean**	**95% CI**	**% Difference, PTSD vs. No PTSD (95% CI)**	**P**
Unadjusted	31.1	24.6 – 39.4	60.6	41.8 – 87.9	+ 95% (30% – 192%)	0.001
Adjusted for socio-demographic factors*	31.6	24.9 – 40.1	59.9	41.1– 87.3	+ 90% (25% – 186%)	0.002
+ service in Southeast Asia	30.9	24.3 – 39.1	64.3	43.9 – 94.1	+ 108% (37% – 217%)	<0.001
+ lifestyle and CHD risk factors†	31.5	24.7 – 40.1	64.2	43.3 – 95.2	+ 104% (31% – 216%)	0.002
+ major depression	31.3	24.5 – 39.9	64.1	42.6 – 96.4	+ 105% (30% – 222%)	0.002
+ other psychiatric diagnoses‡	30.7	24.1 – 39.1	68.5	45.2 – 103.7	+ 123% (41% – 254%)	<0.001

CHD: coronary heart disease; CI: confidence interval; PTSD: posttraumatic stress disorder; STSS: stress total severity score.

469 twins (112 with PTSD) were included in the STSS analysis. Because STSS was not normally distributed, it was log transformed for analysis; results are presented as geometric means and percent differences to improve interpretability.

*Age, education, family income

†Number of alcoholic drinks per day, smoking (never, past, current), physical activity (not active, moderate activity, vigorous activity), history of hypertension

‡ Alcohol or drug abuse or dependence

Table 4. Multivariable analysis of the relationship between PTSD and CFR in the overall sample.

	No PTSD (N=324)		PTSD (N=92)			
Model	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean Difference, PTSD vs. No PTSD (95% CI)**	**P**
Unadjusted	2.51	2.42 – 2.61	2.30	2.14 – 2.46	-0.21 (-0.39 – -0.03)	0.02
Adjusted for socio-demographic factors*	2.51	2.42 – 2.61	2.31	2.15 – 2.48	-0.20 (-0.38 – -0.02)	0.03
+ service in Southeast Asia	2.52	2.42 – 2.61	2.31	2.14 – 2.47	-0.21 (-0.39 – -0.02)	0.03
+ lifestyle and CHD risk factors†	2.51	2.42 – 2.61	2.37	2.20 – 2.53	-0.15 (-0.34 – 0.04)	0.13
+ major depression	2.51	2.42 – 2.61	2.39	2.21 – 2.56	-0.13 (-0.32 – 0.07)	0.20
+ other psychiatric diagnoses‡	2.52	2.42 – 2.61	2.39	2.21 – 2.57	-0.13 (-0.33 – 0.07)	0.22

CHD: coronary heart disease; CFR: coronary flow reserve; CI: confidence interval; PTSD: posttraumatic stress disorder.

416 twins (92 with PTSD) were included in the CFR analysis.

*Age, years of education, family income

†Number of alcoholic drinks per day, current and past smoking, physical activity (not active, moderate activity, vigorous activity), history of hypertension

‡ Alcohol or drug abuse or dependence

Table 5. Relationship between PTSD and CHD outcome measures in PTSD-discordant twin pairs.

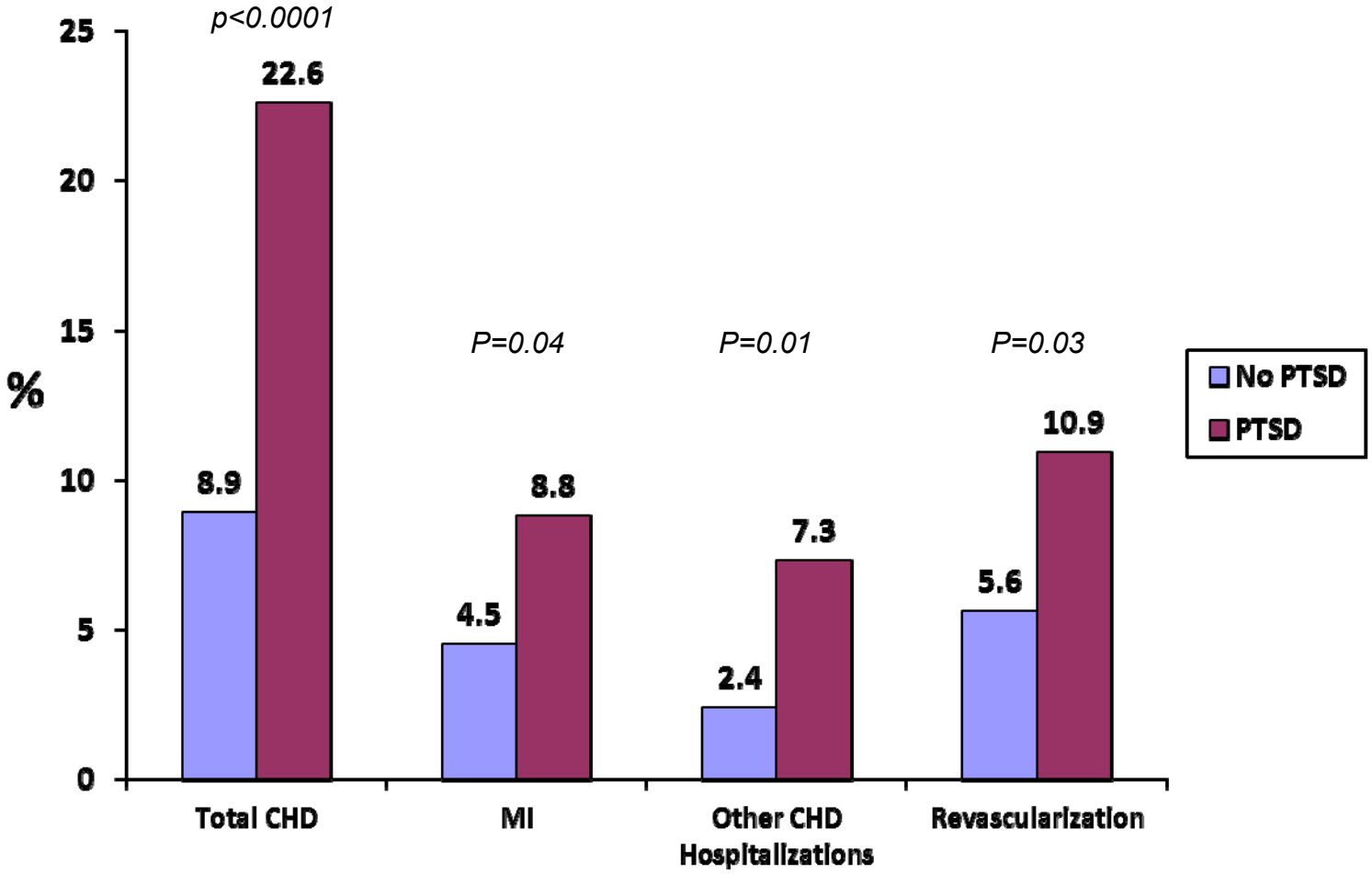
CHD Outcome Measures	No PTSD	PTSD	Estimate (95% CI)	P
Total CHD (117 Pairs)	No. Events (%)		Odds Ratio (95% CI)	
Unadjusted	15 (12.8)	26 (22.2)	1.9 (1.0 – 3.6)	0.04
Adjusted for service in Southeast Asia, lifestyle and CHD risk factors* and other psychiatric diagnoses†	--	--	2.1 (1.0 – 4.3)	0.045
STSS (90 Pairs)	Geometric Mean (95% CI)		% Difference (95% CI)	
Unadjusted	44.0 (28.7 – 67.2)	75.5 (49.2 – 115.9)	+72% (11% – 165%)	0.02
Adjusted for service in Southeast Asia, lifestyle and CHD risk factors* and other psychiatric diagnoses†	44.2 (27.9 – 70.1)	77.9 (49.0 – 123.8)	+76% (1% - 206%)	0.045
CFR (65 Pairs)	Mean (95% CI)		Mean Difference (95% CI)	
Unadjusted	2.44 (2.26 – 2.63)	2.23 (2.04 – 2.42)	-0.22 (-0.42 – -0.02)	0.03
Adjusted for service in Southeast Asia, lifestyle and CHD risk factors* and other psychiatric diagnoses†	2.39 (2.19 – 2.60)	2.33 (2.12 – 2.54)	-0.06 (-0.30 – 0.18)	0.60

CHD: coronary heart disease; CFR: coronary flow reserve; CI: confidence interval; PTSD: posttraumatic stress disorder; STSS: stress total severity score.

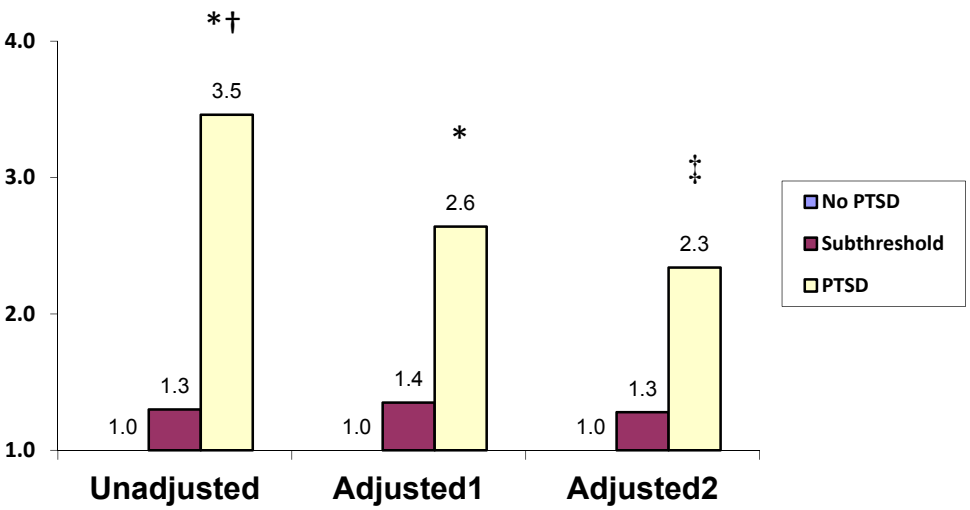
*Number of alcoholic drinks per day, current and past smoking, physical activity (not active, moderate activity, vigorous activity), history of hypertension

† Major depression, and alcohol or drug abuse or dependence

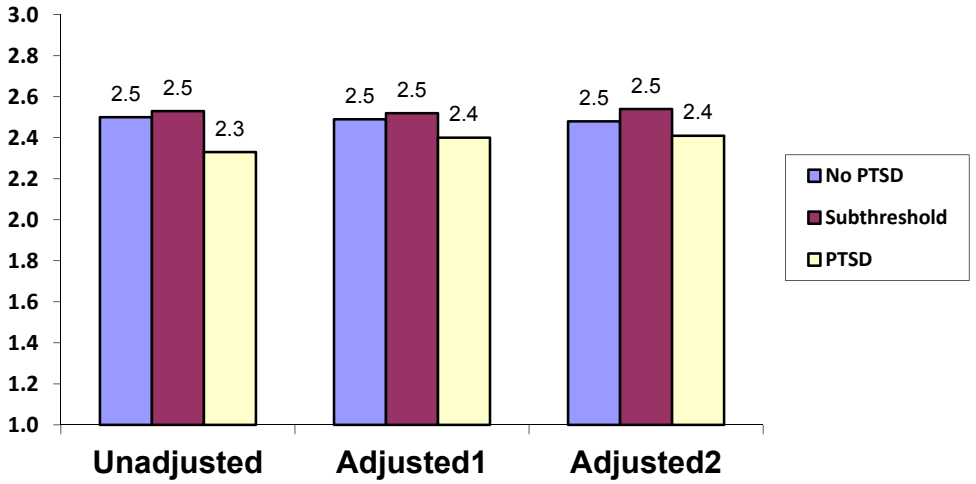
Figure 1


p<0.0001
P=0.04
P=0.01
P=0.03
25
20
15
10
5
0
%
22.6
8.9
8.8
4.5
7.3
2.4
10.9
5.6
No PTSD
PTSD
Total CHD
MI
Other CHD Hospitalizations
Revascularization

OR for CHD



CFR



STSS

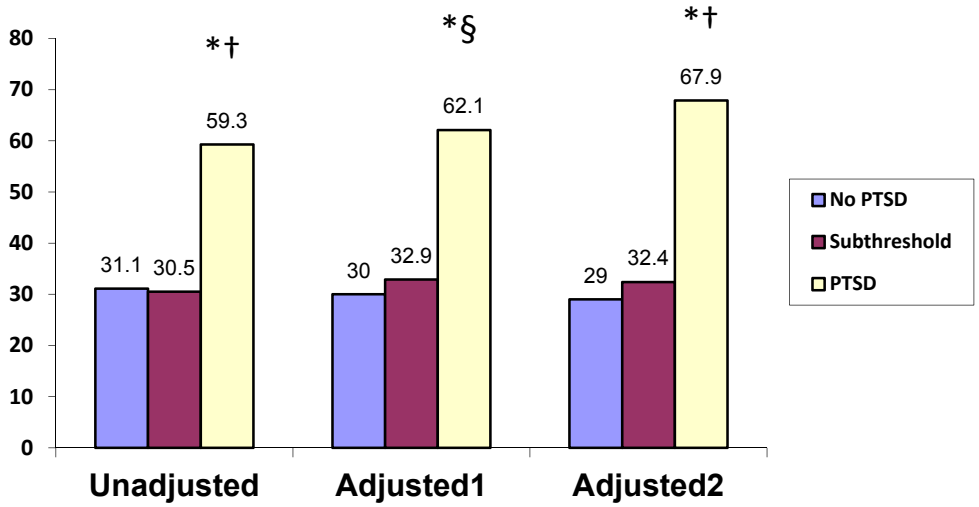
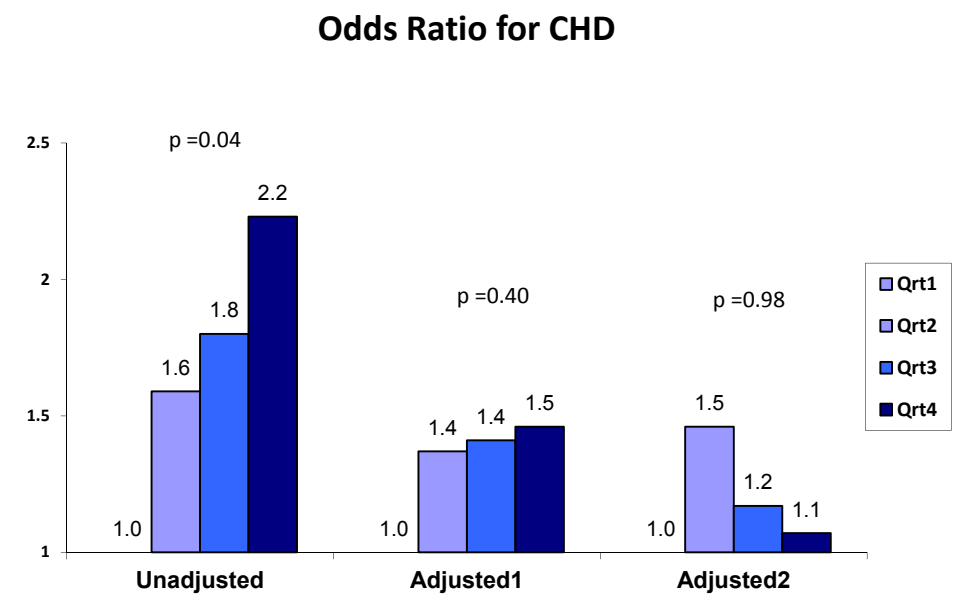
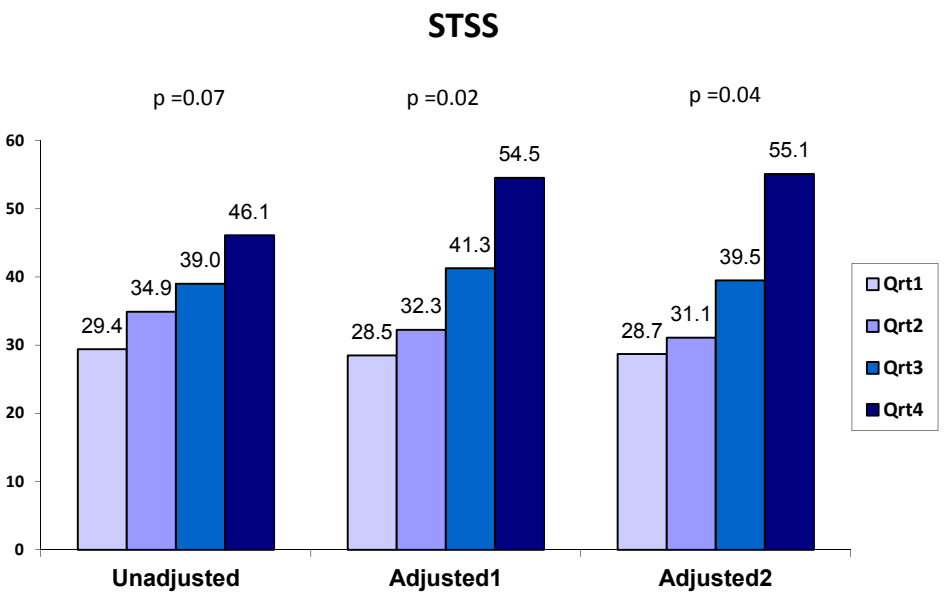
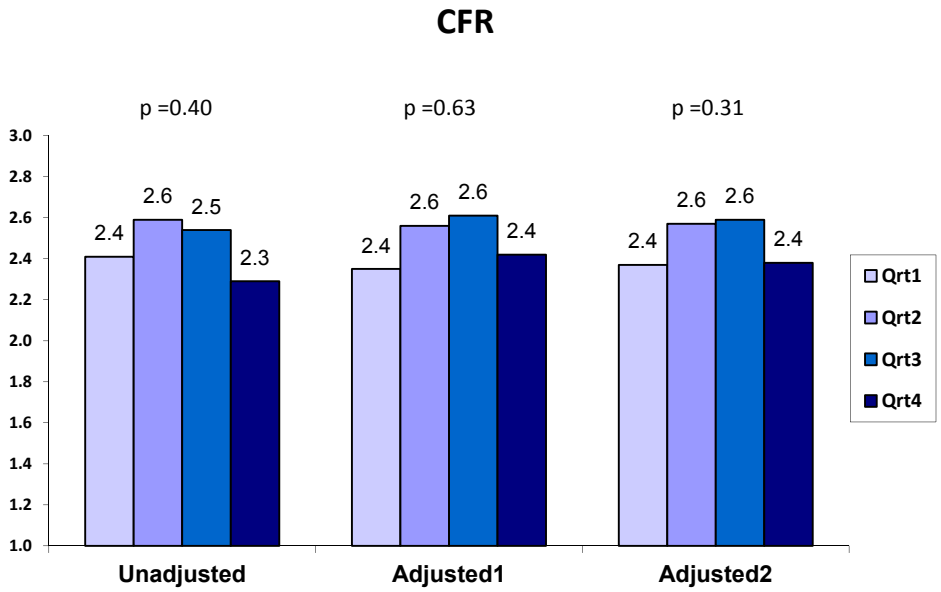


Figure 3


Odds Ratio for CHD
p =0.04
p =0.40
p =0.98
2.5
2
1.5
1
2.2
1.8
1.6
1.0
1.4
1.4
1.5
1.0
1.5
1.2
1.1
1.0
Unadjusted
Adjusted1
Adjusted2
Qrt1
Qrt2
Qrt3
Qrt4


STSS
p =0.07
p =0.02
p =0.04
60
50
40
30
20
10
0
46.1
39.0
34.9
29.4
54.5
41.3
32.3
28.5
55.1
39.5
31.1
28.7
Unadjusted
Adjusted1
Adjusted2
Qrt1
Qrt2
Qrt3
Qrt4


CFR
p =0.40
p =0.63
p =0.31
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
2.4
2.6
2.5
2.3
2.4
2.6
2.6
2.4
2.4
2.6
2.6
2.4
Unadjusted
Adjusted1
Adjusted2
Qrt1
Qrt2
Qrt3
Qrt4