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Post-Traumatic Stress Disorder and Cardiovascular Diseases: A Cohort Study of Men and Women Involved in Cleaning the Debris of the World Trade Center Complex

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BACKGROUND: To determine whether post-traumatic stress disorder (PTSD) is a risk factor for myocardial infarction (MI) and stroke, beyond the expected effects from recognized cardiovascular risk factors and depression.

METHODS AND RESULTS: World Trade Center-Heart is an observational prospective cohort study of 6481 blue-collar first responders nested within the World Trade Center Health Program in New York City. Baseline measures in 2012 and 2013 included blood pressure, weight and height, and blood lipids. PTSD, depression, smoking, and dust exposure during the 2001 cleanup were self-reported. During the 4-year follow-up, outcomes were assessed through (1) interview-based incident, nonfatal MI, and stroke, validated in medical charts (n=118); and (2) hospitalizations for MI and stroke for New York city and state residents (n=180). Prevalence of PTSD was 19.9% in men and 25.9% in women, that is, at least twice that of the general population. Cumulative incidence of MI or stroke was consistently larger for men or women with PTSD across follow-up. Adjusted hazard ratios (HRs) were 2.22 (95% confidence interval [CI], 1.30–3.82) for MI and 2.51 (95% CI, 1.39–4.57) for stroke. For pooled MI and stroke, adjusted HRs were 2.35 (95% CI, 1.57–3.52) in all and 1.88 (95% CI, 1.01–3.49) in men free of depression. Using hospitalization registry data, adjusted HRs were 2.17 (95% CI, 1.41–3.32) for MI; 3.01 (95% CI, 1.84–4.93) for stroke; and for pooled MI and stroke, the adjusted HR was 2.40 (95% CI, 1.73–3.34) in all, HR was 2.44 (95% CI, 1.05–5.55) in women, and adjusted HR was 2.27 (95% CI, 1.41–3.67) in men free of depression. World Trade Center dust exposure had no effect.

CONCLUSIONS: This cohort study confirms that PTSD is a risk factor for MI and stroke of similar magnitude in men and women, independent of depression.
WHAT IS KNOWN

- Post-traumatic stress disorder has been consistently shown to be an independent risk factor for incident myocardial infarction or stroke in cohort studies.
- However, despite the wealth of evidence, post-traumatic stress disorder is still not recognized as a risk factor for cardiovascular disease because available studies are all affected by 1 or several limitations.

WHAT THE STUDY ADDS

- World Trade Center-Heart offers unique and strong evidence that World Trade Center attack–related post-traumatic stress disorder is a risk factor for myocardial infarction and stroke, in men and women, and independent of recognized cardiovascular risk factors and depression.
- Because of its methodological strength (ie, active follow-up, medical chart validation, and adjustment for depression), this study validates previous reports of exclusively male or female cohorts.

This is the first report from World Trade Center (WTC)-Heart—a cohort study specifically designed to assess the association between early response to the WTC September 11 attack and cardiovascular outcomes. WTC-Heart comprises blue-collar workers who were involved in the cleaning of the debris of the WTC complex during the months immediately after the attack. The cohort offers the ability to assess whether post-traumatic stress disorder (PTSD) is involved in cardiovascular disease (CVD) incidence because of 3 cohort characteristics: (1) it underwent the same, extraordinary traumatic event at a discrete point in time and suffers from an excess burden of PTSD symptoms at least twice that of the general population; (2) being nested within a long-term program offering free care to first responders, can explore long-term risk 11 to 15 years after the event; and (3) because first responders were on average in their forties in 2001, it is a relatively young cohort in which CVDs would be expected to be rare if it was not because of this unique exposure to the psychologically and environmentally traumatic event in 2001.

PTSD—a syndrome characterized by re-experiencing the traumatic exposure, avoidance of reminders, hyperarousal, and negative mood and cognitions, highly prevalent among WTC responders—has been consistently shown to be an independent risk factor for incident myocardial infarction (MI) or stroke in cohort studies. Previous reports from a different WTC cohort have related psychological stress to heart diseases among people who worked at or were living in the vicinity of Ground Zero in 2001 to 2002. However, despite the wealth of evidence, PTSD is still not recognized as a risk factor for CVD because available studies are all affected by 1 or several limitations, such as self-report of established CVD risk factors (eg, lipids, blood pressure, weight, and height), self-reported CVD events, exclusively male or female cohorts, or nonadjustment for depression. In contrast, in WTC-Heart, CVD risk factors were measured in a standardized fashion, and incident cases of MI and stroke were assessed using an active follow-up, including personal interviews and validation of events in medical charts simultaneously in men and women.

METHODS

The data, analytic methods, and study materials will not be automatically made available to other researchers for purposes of reproducing the results or replicating the procedure. The cohort is nested within the WTC Health Program (WTCHP), and authorization will have to be obtained from the WTCHP too.

WTC-Heart is a prospective, fixed cohort of 6481 WTC first responders involved in cleaning up the debris of the WTC complex in New York City in 2001 and 2002 and recruited within the WTCHP. Active follow-up for incident and recurrent CVD was conducted from January 2012 until June 2016, remotely via e-mail, mail, and phone interviews in English, Spanish, and Polish. The cohort was also linked with the New York state hospitalization database, SPARCS.

The cohort was recruited from 2 WTCHP sites (ie, the Icahn School of Medicine at Mount Sinai or North Shore Long Island Jewish Hospital) in New York City. The WTCHP, established in 2002, comprises nonfirefighter workers and volunteers engaged in rescue, recovery, restoration of services, cleanup, or other support work on or after September 11. These first responders were eligible in the WTCHP if they had worked for ≥4 hours on September 11 to 14, 2001, ≥24 hours during the month of September 2001, or ≥80 hours total during the period of October through December 2001. Also eligible were employees of the Office of the Chief Medical Examiner who processed human remains, of the Port Authority Trans-Hudson Corporation who participated in the cleanup efforts for ≥24 hours from February to July 2002, and workers who drove, repaired, cleaned, or maintained vehicles that handled WTC debris for at least 1 day between September 11, 2001, and July 31, 2002.

Sample

The cohort is a consecutive sample of 6481 women and men attending one of their s10th annual clinical visits at the WTCHP between January 2012 and June 2013 (baseline). Annual visits are not necessarily associated with medical problems requiring care. Informed consent was provided on the day of recruitment, in English, Spanish, and Polish. The Queens College Institutional Review Board and those of the 2 recruitment sites approved the WTC-Heart protocol.

Exposures

Recognized cardiovascular risk factors comprised: (1) standardized 2 measurements of blood pressure to the third digit...
(eg, 12.2) after sitting down; (2) a comprehensive smoking history; (3) body weight and height measured in lightly dressed subjects; and (4) blood lipids: total cholesterol, low-density lipoprotein, and triglycerides. Clinical personnel were trained specifically for this study and provided identical, new instruments (scales, sphygmomanometers). Baseline mental health symptoms included the PTSD checklist PCL-C (civilian) for DSM-IV,\textsuperscript{15} with a specific preamble relating the answers to the participation in the WTC cleanup. The cutoff for probable PTSD was ≥44 points as recommended given the prevalence of PTSD in the cohort.\textsuperscript{16} Possible depression was defined as a score of ≥10 (in a range of 0–27) on the 9 questions of the Patient Health Questionnaire-9.\textsuperscript{17}

In a detailed questionnaire, each participant indicated: (1) which day on or after September 11 they began working on the WTC complex; (2) whether they were directly in the cloud of dust (or blackout) from the collapse of the WTC buildings or not; (3) whether their work was adjacent or on the pile of dust (or blackout) from the collapse of the WTC buildings; (4) whether they wore a protective mask.\textsuperscript{18}

**Active Follow-Up**

Attempts were made to contact every participant once a year from the 2012 baseline to June 2016. At each annual contact, incident cardiac and incident neurological events were reported in a standardized, self-administered survey in English, Spanish, and Polish either online, by mail, or by telephone. In case of death reported by a relative or by the WTC Health Program, a questionnaire and request of death certificate was mailed to either relatives or healthcare provider.

**Outcomes**

All self-reported CV events on the follow-up forms, including positive report of cardiac symptoms, MI, neurological symptoms, or stroke, were tentatively confirmed by specific additional personal interviews conducted by phone by trained interviewers in English, Spanish, or Polish. Determination of incident and recurrent cardiovascular outcomes in medical charts was performed by a blinded adjudicating panel comprising the principal investigator (A.M.) and a senior research worker (C.M.-M.) with 24 years of experience adjudicating acute MI and stroke in several large population-based studies. An MI was confirmed in the presence of typical symptoms, EKG signs, troponin, and enzymatic movement. A stroke or a transient ischemic attack was confirmed in the presence of typical symptoms and medical imaging or sonographic signs.

From January 1, 2012, through December 31, 2016, (the latest year available) all WTC-Heart participants were electronically linked to New York State Department of Health SPARCS program, which includes diagnoses and dates for all patients discharged from acute care hospitals, excluding psychiatric and federal hospitals. The coding of discharge diagnoses may not be accurate, but the degree of inaccuracy is likely to be homogeneous across the cohort. Matched records had identical key identifying information, such as name, date of birth, last 4 digits of the social security number, or address. Analyses were restricted to the 5484 New York city or state residents. We used, for MI, *International Classification of Diseases, Ninth Revision* codes 410 to 411 and *International Classification of Diseases, Tenth Revision* codes I21-I22, and for stroke, *International Classification of Diseases, Ninth Revision* codes 430 to 432 and *International Classification of Diseases, Tenth Revision* codes I60-I63. For the follow-up years 2012 through 2016, 180 WTC-Heart study participants were identified in the SPARCS database as having been hospitalized with a discharge diagnosis of MI or stroke.

**Statistical Analysis**

Kaplan-Meier survival analysis was used to plot the cumulative incidence of MIs and stroke. Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of MI or stroke, adjusted for use of a respirator and for recognized cardiovascular risk factors: age, blood pressure, total cholesterol, body mass index, tobacco use, and, when relevant, sex. Firth procedure was applied to improve aHR and CI estimates from Cox proportional hazard models with small sample sizes and few measured outcome events.\textsuperscript{19}

Because PTSD may have increased weight gain, tobacco use, blood pressure, and possibly cholesterol after the 2001 to 2002 trauma, resulting in these factors being on the pathway to MI and stroke and biasing the hazard ratios (HRs) toward the null, we present primary analyses both age adjusted and, when sample size allows, adjusted for all these factors.

Time of event was retrieved from the participant’s interview or SPARCS records. For event-free participants censoring for interview-based incident, events occurred at the date of completion of the most recent annual survey, or, for SPARCS-derived events, on December 31, 2016—the last date of available SPARCS data. Analyses of postbaseline, incident outcomes were, therefore, repeated including and excluding MIs and strokes recurring during follow-up among subjects who already had an MI or stroke before 2012. We report the analysis including all cases in the article for 4 reasons: (1) because this cohort had a mean age of 51 years in 2012, all cardiovascular events occurred after 2001; (2) PTSD is a chronic disease, most likely secondary to 2001, for which it is difficult to set an exact date of onset; (3) these middle aged subjects who had cardiovascular events before baseline were subjects at the highest risk in the cohort and excluding them would also introduce selection bias; (4) removing 35 recurrent cases did not alter the statistical power for the full analysis (as shown in the article) but left thin data for the sex- and disease-specific analyses. Thus, subjects who had had prebaseline cardiovascular events were excluded for some of the exploratory full sample analyses but kept in all other analyses, with only the postbaseline events going into the numerator of the hazard rates and risks.

MI and stroke were analyzed both separately and pooled as a single outcome (MI/stroke) because separate analyses of self-reported MI and stroke, provided in an appendix, yielded associations of consistent magnitudes. Similarly, men and women were analyzed estimating both separate and pooled sex-adjusted HRs. The number of female cases (9 MIs, 7 strokes, and 22 hospitalizations for MI or stroke) precluded statistical power for most analyses, but, as shown in the appendix, the magnitude of the associations was remarkably consistent across sex allowing for meaningful sex-adjusted
HRs. The participants who had both MI and stroke were analyzed as per the first of the 2 outcomes in the analyses pooling MI and stroke.

Because PTSD and depression are highly correlated, the analyses for pooled MI and stroke adjusted for recognized cardiovascular risk factors were repeated among 4120 non-depressed men (the number of female cases was too small to perform sex-adjusted analyses), after exclusion of men having either depression only (n=97), depression and PTSD (n=477), or missing depression data (n=248).

RESULTS

The sociodemographic, cardiovascular, and mental characteristics of the WTC-Heart cohort were similar to those of the whole WTCHP in which it was nested (Table I in the Data Supplement). As of July 1, 2016, 510 participants (7.9%) had no follow-up information. The analyses are, therefore, based on 4942 men and 1029 women (n=5971).

Baseline (2012–2013) Characteristics

Mean age was 51.3 years in men and 51.1 years in women. The cohort was 82.8% men, 54.1% white, and 25.4% lower than college education. The Table shows these characteristics by sex. Prevalence of PTSD was 19.9% in men and 25.9% in women.

Recognized Cardiovascular Risk Factors and Dust

Figure 1 and Table II in the Data Supplement show current smoking standing out—besides PTSD not shown in Figure 1—as the main recognized risk determinant of incident (including recurrent) pooled MI and stroke, after adjustment for other cardiovascular risk factors and PTSD. Specific results for MI or stroke are shown in Tables III and IV in the Data Supplement. Moreover, resting heart rate per minute at baseline was, respectively, for those without and with PTSD, 68.9 and 70.8 in men and 69.5 and 69.9 in women (not shown in a table).

None of the variables differently expressing the timing or intensity of exposure to the WTC dust and dust cloud were independently associated with subsequent MI or stroke in these analyses (Table V in the Data Supplement). Donning of a protective mask was deemed the closest approximation of the amount of dust inhaled and was adjusted for in all multivariate analyses (Figure 1).

Cumulative Risk of CVD by PTSD

By June 30, 2016, reported cases were 70 MIs, of which 20 were recurrent, and 53 strokes, of which 15 were recurrent. Figure 2 shows the cumulative risks of MI and stroke for the whole sample by PTSD status. The curves diverge early, divergence increases over time, with statistically significant differences at \( P<0.0001 \). Specific
Risk Factors | Comparisons | aHR
---|---|---
Blood Pressure | High/Normal | 1.25
Total Cholesterol | High/Normal | 1.19
BMI | Overweight/Normal | 1.28
Obese/Normal | 1.32
Cigarettes | Former/Never | 1.01
Current/Never | 2.33
Used Respirator | yes/no | 0.95

*Adjusted for use of a respirator and for recognized cardiovascular risk factors: age, blood pressure, total cholesterol, body mass index (BMI), tobacco use, and, when relevant, sex.

Figure 1. Adjusted* hazard ratios (aHRs) of pooled incident (including recurrent) myocardial infarctions and strokes and recognized risk factors in the World Trade Center-Heart cohort (n=5971)—New York, 2012 to 2016.

Multivariable Analysis

In Figure 3 and Table VI in the Data Supplement the aHRs of PTSD were 2.22 (95% CI, 1.30–3.82) for 70 MIs, 2.51 (95% CI, 1.39–4.57) for 53 strokes, 2.35 (95% CI, 1.57–3.52) for 118 incident (including recurrent) pooled MI and stroke, and (not shown in a table or figure) 2.24 (95% CI, 1.39–3.63) for 83 incident (excluding recurrent) pooled MI and stroke. Five subjects had both MI and stroke. Specific results by sex and outcomes are provided in Table VI in the Data Supplement. In women, the estimated HRs for MI, stroke, and pooled MI and stroke were consistent with those observed among men.

Misclassification of Outcomes

Access to medical charts to validate the interview-based diagnosis was similar in cohort participants with (60%) and without PTSD (62%). The confirmation fraction was also similar across groups for stroke. However, for MIs, it was smaller for PTSD (47%) than for non-PTSD cases (74%). Such source of differential misclassifica-
tion could spuriously strengthen the observed associations. We, therefore, repeated the analyses using discharge diagnoses for hospitalization in New York State for MI or stroke as outcomes—a measure independent of participant reports.

**Hospitalization for MI or Stroke**

These analyses were restricted to New York city or state residents (n=5484). All incident MI and strokes identified in interviews, whether confirmed or not in medical charts, were present in the SPARCS database. In contrast, 49 events (19 among subjects with PTSD and 30 among subjects without PTSD) were recorded in SPARCS but had been missed by the active follow-up. As shown in Figure 4 and Table VII in the Data Supplement for hospitalizations for MI or stroke in New York, aHRs were 2.17 (95% CI, 1.41–3.32) for 112 MIs, 3.01 (95% CI, 1.84–4.93) for 77 strokes, and 2.40 (95% CI, 1.73–3.34) for pooled 180. Nine subjects had been hospitalized for both MI and stroke. The association of PTSD and hospitalization for pooled MI and stroke adjusted for age only was statistically significant among women too (HR, 2.44; 95% CI, 1.05–5.55).

Of note, of the 415 lost to active follow-up, 228 (54.9%) had a record in SPARCS between January 2012 and December 2016. Of these 228, 4 had had an MI or a stroke, that is, 1.8% (95% CI, 0.0–3.5). This cumulative incidence of hospitalizations for MI or stroke in the lost to follow-up is of the same order of magnitude as that of 2.8% observed in the full cohort of (123/5971) during the same period.

**Control of Depression**

In the full cohort, there were 6 cases of MI or stroke in men with depression but no PTSD and 29 cases of MI or stroke in men with both depression and PTSD. Among men free of depression, the crude (not shown in the figures), age-adjusted, and multivariate (shown in Figures 3 and 4) HRs of MI or stroke were, respectively, 1.94 (95% CI, 1.07–3.50), 2.19 (95% CI, 1.21–3.95), and 1.88 (95% CI, 1.01–3.49) for incidence and 1.93 (95% CI, 1.19–3.02), 2.41 (95% CI, 1.49–3.75), and 2.27 (95% CI, 1.41–3.67) for hospitalization.

**Mortality**

There were 43 deaths identified in the cohort, of which 3 were from CVDs, 18 from other causes, and 22 from unknown causes.

**PCL Score**

When using the continuous PCL-C score instead of the dichotomized PTSD variable, the aHR of pooled MI or
stroke for each SD increase in PCL score was identical for both incident events and for hospitalizations: 1.58 (95% CI, 1.35–1.84) including recurrent cases and 1.36 (95% CI, 1.17–1.95) excluding recurrent cases.

**DISCUSSION**

After 4 years of active follow-up of WTC-Heart, PTSD comes out as a strong, independent determinant of MI and stroke, in both men and women, before and after controlling for recognized use of a respirator during cleanup of debris, cardiovascular risk factors, and depression. Consistent HRs were observed when restricting the analyses to discharge diagnoses of MI and stroke derived from linkage to a New York hospital registry and, therefore, independent of patient reports. Because of its methodological strength (ie, active follow-up, medical chart validation, and adjustment for depression), this study validates previous reports of exclusively male or female cohorts and those of the WTC-Registry reports. The independence of the PTSD and MI or stroke association from depression is consistent with most but not all reports.

**PSTD and CVD in Women**

The associations with PTSD were in the same order of magnitude for men and women, and, specifically, the association of PTSD and hospitalization for pooled MI and stroke was statistically significant in both sexes. Of the 3 previous cohort studies that examined women, 2 had only women, and 1 lacked measured conventional cardiovascular risk factors. The average ages of women at baseline in these 3 cohorts were 44.4, 34, and 32 years, whereas women in WTC-Heart were 51.1 years of age at baseline. Thus, the present...
results add qualitatively to the evidence indicating that PTSD before menopause increases women’s long-term risk of MI and stroke.22

**Biological Plausibility**

PTSD is a polythetic disorder consisting of clusters of symptoms potentially impacting cardiometabolic risk.23,24 For example, PTSD may develop and persist because of fear manifested by nightmares, intense emotional and physiological re-experiencing of the trauma, active avoidance of cues or reminders of the trauma, and exaggerated startle response to threat.25 Another cluster groups symptoms evoking major depression, such as anhedonia, detachment, restricted affect, sleep difficulty, and failing concentration.26–28 In humans, the stress associated with these PTSD dimensions may upregulate amygdalar activity, activating both the sympathetic nervous system, releasing inflammatory cells from the bone marrow, and leading to atherosclerotic inflammation, MI, and stroke.29–36 The similar effect sizes in this study suggest similar mechanisms relating PTSD and incident MI or stroke in men and women.37

**Recognized Cardiovascular Risk Factors**

Current smoking was the only recognized cardiovascular risk determinant in this cohort. Blood lipids, blood pressure, and body mass were not associated with MI or stroke. These recognized risk factors may play a role for individual cohort members, but they do not discriminate cardiovascular risk in this homogeneous cohort of blue-collar workers.

Because PTSD is more prevalent in this cohort (20.9%) than current smoking (7.1%) for aHRs of a similar magnitude of 2, ≈3x more cardiovascular cases are attributable to PTSD than to current smoking.
Dust Exposure

None of the variables expressing exposure to the WTC dust, such as the timing and intensity of exposure to the dust cloud or the donning of a protective mask, were independently associated with subsequent MI or stroke in these analyses.

Limitations

The exposure severity and cardiovascular profile of the subcohort of survivors enrolled in the WTC-Heart subjects may not be representative of the estimated 90,000 individuals who originally responded to the September 11 disaster (Figure 5). However, given the homogeneity of the cohort of blue-collar worker in terms of cardiovascular risk, the selection process is unlikely to have biased the risk comparison among the enrollees between those who developed PTSD and those who did not. Moreover, the small losses to follow-up (7.9%) offer some protection against selection bias, in particular because we could estimate that (1) the proportion of lost to follow-up was identical in men (7.9%) and women (7.7%), (2) the subjects lost to follow-up had a similar cardiovascular risk profile as those who remained in the cohort (Table VIII in the Data Supplement), and (3) the cumulative risk of MI and stroke for more than half of those who were never contacted after baseline but had a record in the New York State SPARCS program was of the same order of magnitude as the risk of the rest of the cohort.

We were not able to obtain the causes of death for 22 participants and do not know which proportion of the lost to follow-up died of CVDs. Incorporating cardiovascular deaths could have attenuated or exacerbated the present findings. However, the small number of cardiovascular deaths expected given the age distribution of the cohort is unlikely to have qualitatively modified the cumulative risks of events, which progressively diverged over time between participants with and without PTSD (Figure 2).

Also, because participants were sampled consecutively among subjects attending the WTCHP either for their annual visit or for health problems, we may have included people visiting the clinic more frequently because of poorer health problems than those only visiting the clinic once per year. However, as shown in Table I in the Data Supplement, the demographics of WTC-Heart were virtually identical to those of the whole WTCHP in which it was nested. Prevalences of PTSD in WTC-Heart were almost identical to those published for the whole WTCHP.

Additional limitations include a self-report of PTSD based on the PCL-C questionnaire, residual confounding from self-report of depression based on the Patient Health Questionnaire-9 and recall of respirator use and exposure to the dust cloud, and the lack of assessment of potential biological mediators and unmeasured confounding (eg, prior trauma) of the association between PTSD and MI/stroke. However, similar baseline heart rate for those with and without PTSD spoke against specific protective factor against PTSD in a subgroup of the cohort.

Strengths

Because WTC-Heart is nested within the health program (ie, WTCHP) begun 1 year after the attack and currently providing lifetime free medical care for WTC-related medical conditions to first responders, the cohort study had a unique opportunity to recruit exposed workers 11 to 15 years after September 11 as they entered ages at which incidence of CVD increases rapidly and follow them up for 4 years with small losses (7.9%).

In agreement with previous WTC reports, prevalence of PTSD in this cohort comprising a majority of nontrained responders was more than twice of that in the general population. This excess prevalence of PTSD provided statistical power to study the association of

Figure 5. Flowchart and timeline of the World Trade Center (WTC) Health Program (WTCHP) and of WTC-Heart, 2001 to 2016.
PTSD and cardiovascular outcomes in both sexes. The young age of the cohort participants, associated with low rates of MI or stroke, negatively affected statistical power but allowed us to reasonably assume that few cases were missed during the 2001 to 2012 period. The young age may also have facilitated singling out the effect of PTSD for lack of competing causes.

In terms of validity and confounding controls, analyses were performed before and after adjustment for measured recognized cardiovascular risk factors; in men, the association was observed in the subgroup free of depression; interview-based outcomes were tentatively confirmed in medical charts; findings for interview-based diagnoses of incident MIs and stroke were reproduced after linkage to hospitalization records.

Conclusions
Because of its design, this cohort study offers unique and strong evidence that WTC attack–related PTSD is a risk factor for MI and stroke, in men and women, and independently of recognized cardiovascular risk factors and depression.

REFERENCES


Remch et al; PTSD and Cardiovascular Diseases in Men and Women


