

ORIGINAL ARTICLE

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

BACKGROUND: We sought 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.

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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^{1,2}; (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 responders³—has been consistently shown to be an independent risk factor for incident myocardial infarction (MI) or stroke in cohort studies.^{4–10} 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.^{11,12} 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 2001.¹³ 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, 2002.¹⁴

Sample

The cohort is a consecutive sample of 6481 women and men attending one of their annual clinical visits, up to their 10th annual visit, 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,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.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-9.¹⁷

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 or pit, terms that referred to the former location of the twin towers of the WTC complex; and (4) whether they wore a protective mask.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 WTCHP, 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.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 pre-baseline 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

Table. Baseline Characteristics of Men and Women Comprising the World Trade Center–Heart Cohort (n=5971)—New York, 2012 to 2016

Characteristics	Categories	Men		Women	
		n	%	n	%
Total		4942	100	1029	100
Race	White	2857	57.8	372	36.2
	Black	669	13.5	240	23.3
	Missing	1141	23.1	348	33.8
Ethnicity	Hispanic	1338	27.1	432	42.0
	Missing	96	1.9	19	1.9
Responder	Trained	2077	42.0	424	41.2
	Nontraditional	2359	47.7	517	50.2
	Missing	506	10.2	88	8.6
Smoking	Never	2688	54.4	611	59.4
	Current	351	7.1	64	6.2
	Former	1383	28.0	240	23.2
	Missing	520	10.5	114	11.1
Protective mask on September 11	Donned	4334	87.7	825	80.1
	Missing	99	2.0	23	2.2
Blood pressure	High (systolic >140 or diastolic >90 mm Hg)	1098	22.2	124	12.1
	Missing	143	2.9	47	4.6
Total cholesterol	High (>6.2 mmol/L)	517	10.5	146	14.2
	Missing	NA	NA	NA	NA
HDL	Low (men, <1 mmol/L; women, <1.3 mmol/L)	1069	21.6	527	51.2
	Missing	608	12.3	115	11.2
BMI	Normal (<25 kg/m ²)	458	9.3	258	25.1
	Overweight (25–29.9 kg/m ²)	2012	40.7	382	37.1
	Obese (30+ kg/m ²)	2472	50.0	389	37.8
	Missing	NA	NA	NA	NA
PTSD	Yes	984	19.9	266	25.9
	Missing	NA	NA	NA	NA
Depression	Yes	574	11.6	185	18.0
	Missing	248	5.0	59	5.7
Menopause	Yes	420	40.8
	Missing	2	0.2
Education	College graduates	1319	26.7	379	36.8
	Missing	570	11.5	112	10.9

BMI indicates body mass index; HDL, high-density lipoprotein; NA, not available; and PTSD, post-traumatic stress disorder.

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

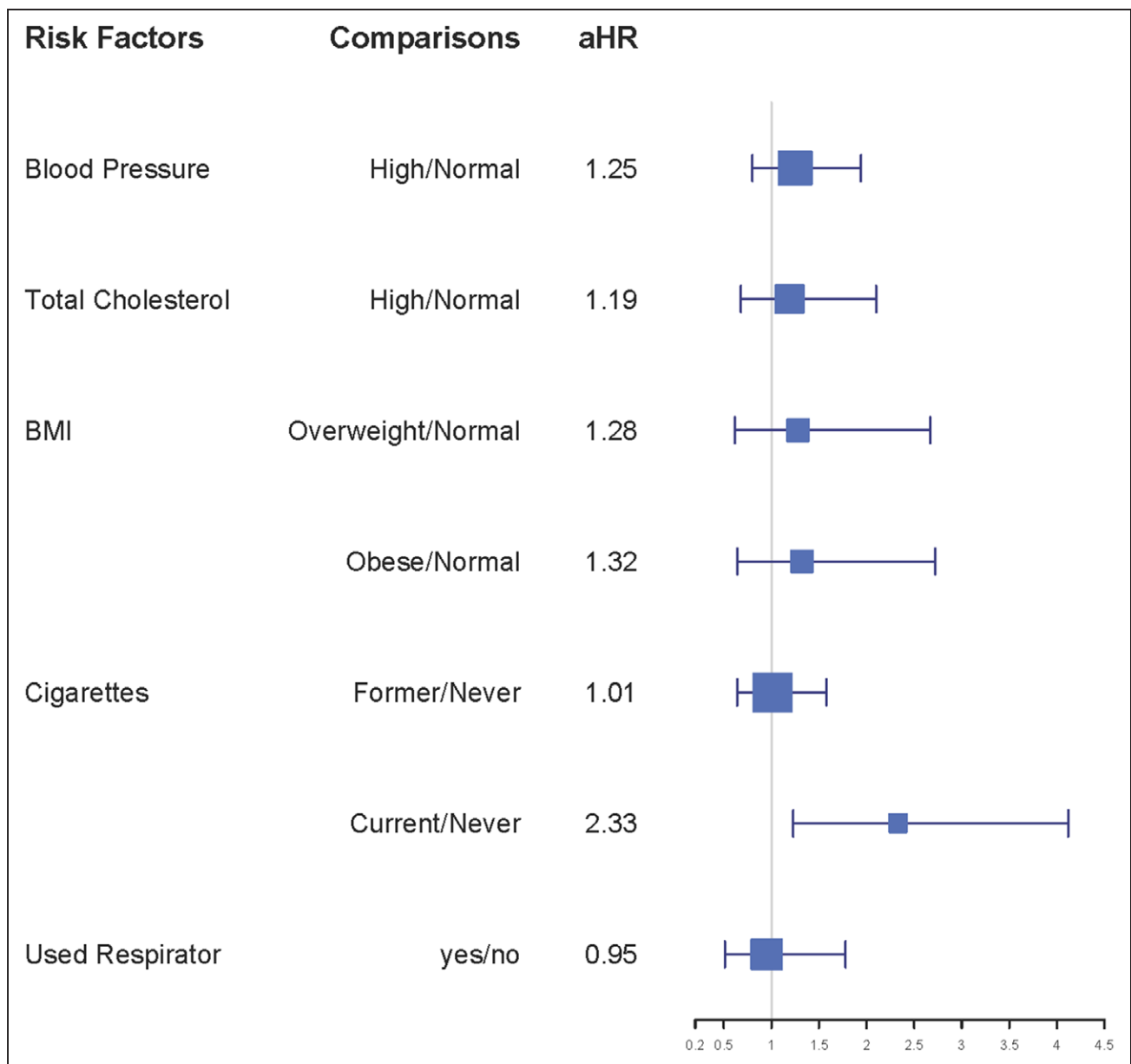


Figure 1. Adjusted* hazard ratios (aHRs) of pooled incident (including recurrent) myocardial infarctions and strokes and recognized risk factors in the World Trade Center–Heart cohort (n=5971)—New York, 2012 to 2016.

*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.

curves for MI or stroke by sex are shown in Figures I through IV in the [Data Supplement](#).

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-

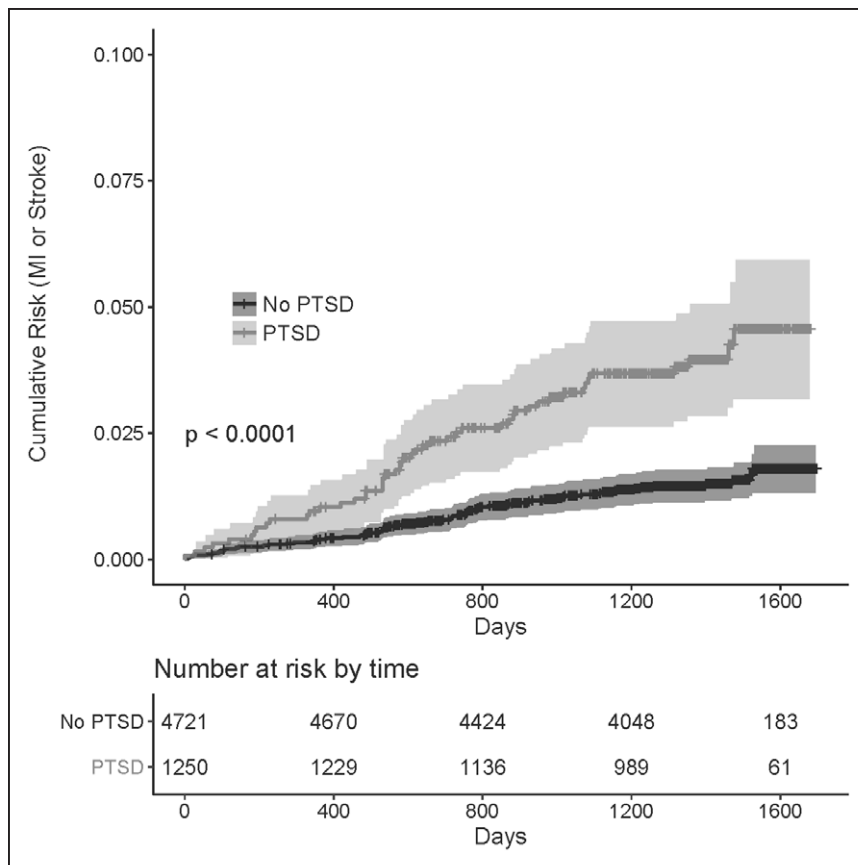


Figure 2. Cumulative risk of pooled incident (including recurrent) myocardial infarctions and strokes by post-traumatic stress disorder (PTSD) status in the World Trade Center-Heart cohort (n=5971)—New York, 2012 to 2016. MI indicates myocardial infarction.

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 cumula-

tive 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

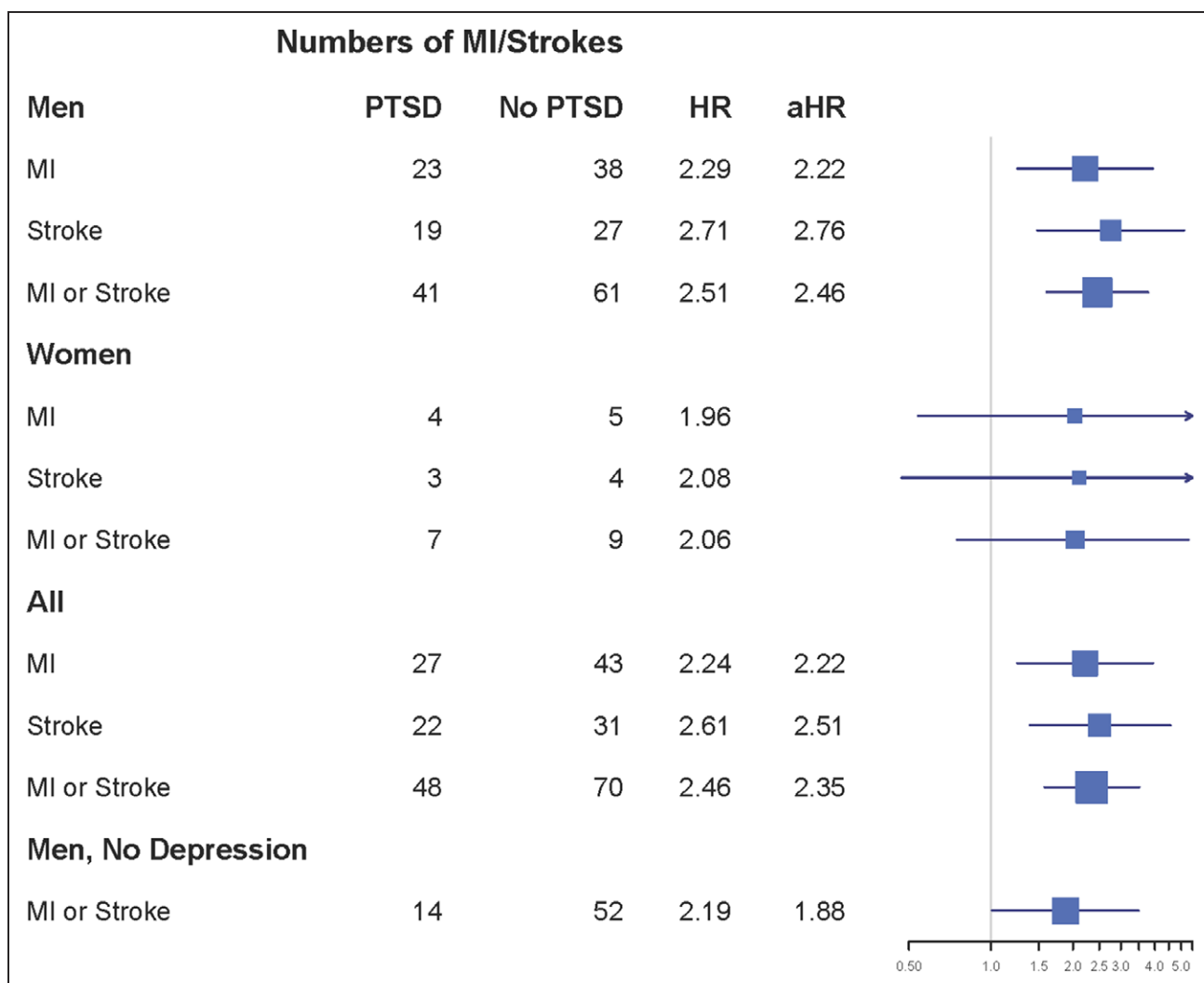


Figure 3. Age-adjusted hazard ratio (HR) and adjusted* HR (aHR) for post-traumatic stress disorder (PTSD) and pooled incident (including recurrent) myocardial infarctions and strokes in the World Trade Center–Heart cohort (n=5971)—New York, 2012 to 2016.

*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. MI indicates myocardial infarction.

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. Hazard ratios were consistent when analyses were restricted to discharge diagnoses of MI and stroke derived from a New York hospital registry that did not include any patient self-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^{4,5} and those of the WTC-Registry reports.^{11,12} The independence of the PTSD and MI or stroke association from depression is consistent with most⁴ but not all reports.^{20,21}

PTSD 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,^{7,10} and 1 lacked measured conventional cardiovascular risk factors.^{11,12} The average ages of women at baseline in these 3 cohorts were 44.4,⁷ 34,¹⁰ and 32 years,¹² whereas women in WTC-Heart were 51.1 years of age at baseline. Thus, the present

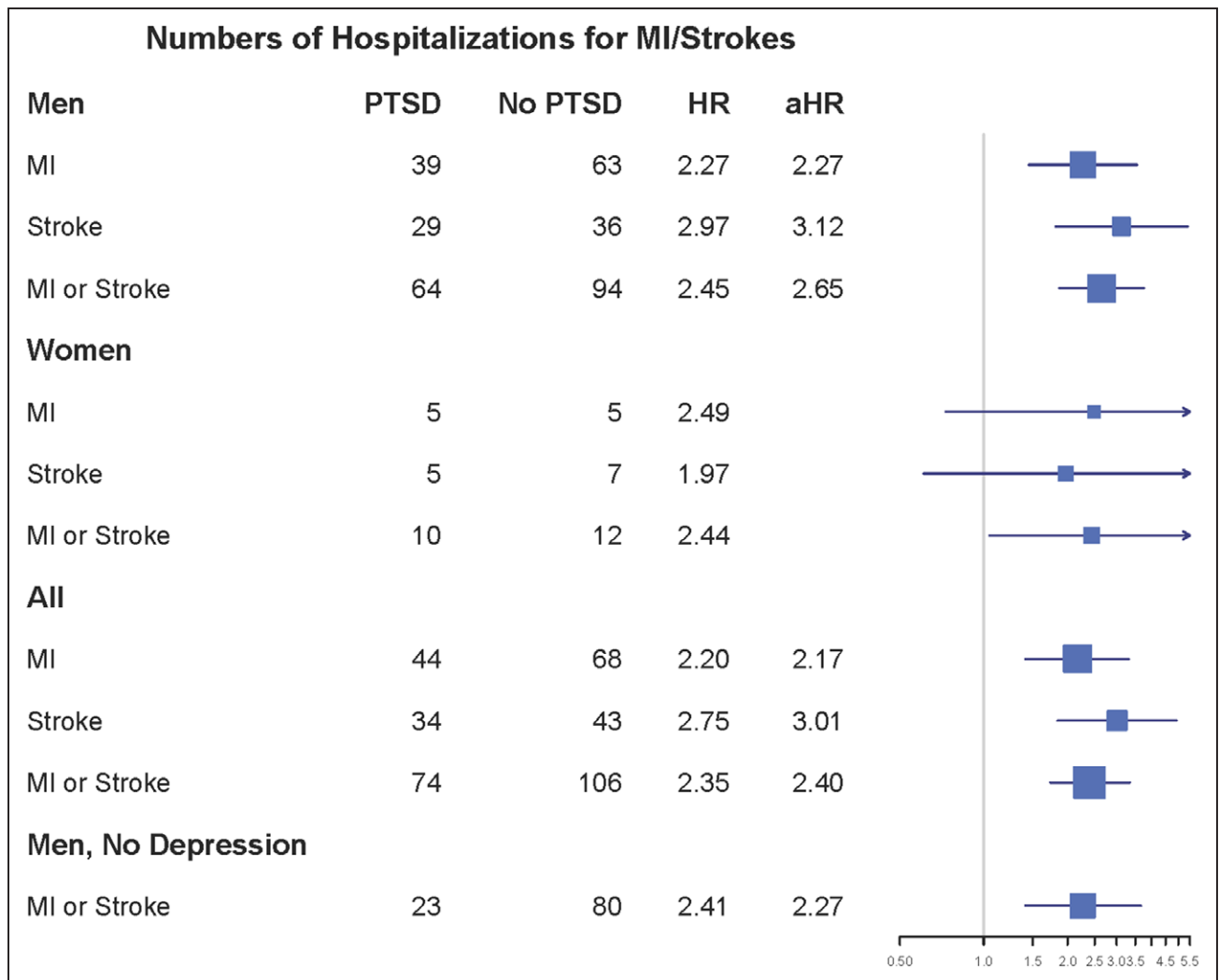


Figure 4. Age-adjusted hazard ratio (HR) and adjusted* HR (aHR) for post-traumatic stress disorder (PTSD) and hospitalizations for pooled (including recurrent) myocardial infarctions and strokes in the World Trade Center–Heart cohort (n=5484)—New York, 2012 to 2016.

*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. MI indicates myocardial infarction.

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 inflam-

matory 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, ≈3× more cardiovascular cases are attributable to PTSD than to current smoking.

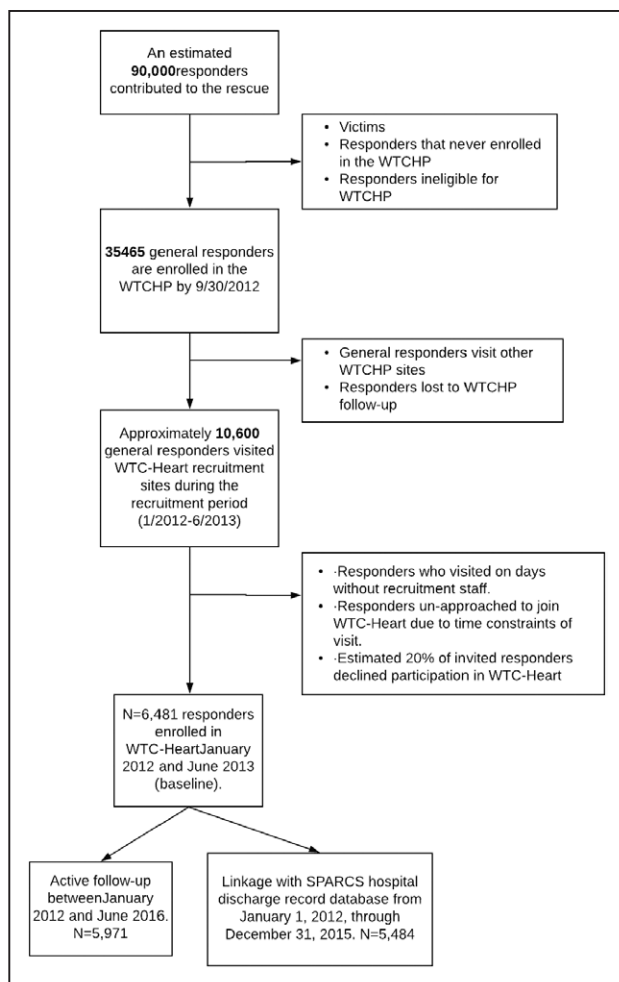


Figure 5. Flowchart and timeline of the World Trade Center (WTC) Health Program (WTCHP) and of WTC-Heart, 2001 to 2016.

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 establish 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.³⁸

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 suggests no specific factor that protects against both PTSD and MI/stroke.

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,³ 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 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.

ARTICLE INFORMATION

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Disclosures

None.

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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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SUPPLEMENTAL MATERIAL

Table S1: Characteristics of WTC General Responder Cohort ($N= 33\ 076$) and WTC-Heart ($N= 6481$)

Table S2: Hazard ratios of incident (including recurrent) MI or stroke, recognized cardiovascular risk factors, and WTC exposure in 4942 men and 1029 women comprising WTC-Heart, New York, 2012-2016.

Table S3: Hazard ratios of incident (including recurrent) MI, recognized cardiovascular risk factors, and WTC exposure in 4942 men and 1029 women comprising WTC-Heart, New York, 2012-2016.

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Table S8: Recognized cardiovascular risk factors and WTC exposure among 4942 men and 1029 women followed up and 424 men and 86 women lost to follow-up. WTC-Heart, New York, 2012-2016.

Figure S1: Cumulative risk of incident (including recurrent) myocardial infarction (MI) by PTSD status in men of the WTC-Heart cohort, New York, 2012-2016.

Figure S2: Cumulative risk of incident (including recurrent) stroke by PTSD status in the WTC-Heart cohort men, New York, 2012-2016.

Figure S3: Cumulative risk of incident (including recurrent) myocardial infarction (MI) by PTSD status in women of the WTC-Heart cohort, New York, 2012-2016.

Figure S4: Cumulative risk of incident (including recurrent) stroke by PTSD status in the WTC-Heart cohort women, New York, 2012-2016.

Table S1: Characteristics of WTC General Responder Cohort ($N = 33\,076$) and WTC-Heart ($N=6\,481$)

Variable	General Cohort in 2014	WTC-Heart in 2013
<i>N</i>	33 076	6 481
Mean age (SD) in years		
On 11 September 2001	38.69 (8.8)	39.48 (8.8)
At Visit 1	43.82 (9.1)	44.35 (8.9)
Age Groups at Visit 1: <i>n</i> (%)		
20 to 24	217 (0.7)	28 (0.4)
25 to 29	1138 (3.4)	181 (2.8)
30 to 34	3424 (10.4)	639 (9.9)
35 to 39	6330 (19.1)	1155 (17.8)
40 to 44	7620 (23.0)	1528 (23.6)
45 to 49	6064 (18.3)	1198 (18.5)
50 to 54	4043 (12.2)	834 (12.9)
55 to 59	2421 (7.3)	563 (8.7)
60 to 64	1206 (3.7)	235 (3.6)
65 and older	613 (1.9)	120 (1.9)
Sex: <i>n</i> (%)		
Female	4759 (14.4)	1115 (17.2)
Male	28 317 (85.6)	5366 (82.8)
Race: <i>n</i> (%)		
African American	3448 (10.4)	1013 (15.6)
Asian/Pacific Islander	461 (1.4)	109 (1.7)
White	18 760 (56.7)	3465 (53.5)
Other	1030 (3.1)	271 (4.2)

Unknown	9377 (28.4)	1623 (25.0)
Hispanic: <i>n</i> (%)	7259 (21.9)	1909 (29.4)
Primary language		
English <i>n</i> (%)	28 376 (85.8)	5673 (87.5)
Marital status: <i>n</i> (%)		
Married or partnered	20 561 (62.2)	3876 (59.8)
Education: <i>n</i> (%)		
< High school graduate	2305 (7.0)	485 (7.5)
High school graduate	6781 (20.5)	1162 (17.9)
Some college	11 831 (35.8)	2281 (35.2)
College graduate	8213 (24.8)	1808 (27.9)
Unknown	3946 (11.9)	745 (11.5)
Monitoring visits (SD)	3.4 (2.1)	4.1 (1.8)

Table S2: Hazard ratios of incident (including recurrent) MI or stroke, recognized cardiovascular risk factors and WTC exposure in 4942 men and 1029 women comprising WTC-Heart, New York, 2012-2016.

Gender		Categories#	No of MI/Stroke	aHR*	95% CI	
					LL	UL
Men	All		102			
	Blood Pressure	Normal	70	1.00	Ref	
		High	31	1.19	0.74	1.89
	Total cholesterol	Normal	83	1.00	Ref	
		High	15	1.33	0.73	2.40
	BMI	Normal	9	1.00	Ref	
		Overweight	38	1.02	0.47	2.21
		Obese	55	1.12	0.53	2.40
	Smoker	Never	44	1.00	Ref	
		Current	17	2.65	1.48	4.74
		Former	31	1.04	0.65	1.68
	Used respirator	No	13	1.00	Ref	
		Yes	87	0.89	0.48	1.88

Women	All		16			
	Blood Pressure	Normal	4	—**	—	
		High	12	—	—	
	Total cholesterol	Normal	14	—	—	
		High	1	—	—	
	BMI	Normal	1	—	—	
		Overweight	8	—	—	
		Obese	7	—	—	
	Smoker	Never	8	—	—	
		Current	1	—	—	
		Former	3	—	—	
	Used respirator	No	2	—	—	
		Yes	12	—	—	
All***	All		118			
	Blood Pressure	Normal	82	1.00	Ref	
		High	35	1.25	0.80	1.94

Total cholesterol	Normal	102	1.00	Ref	
	High	16	1.19	0.68	2.10
BMI	Normal	10	1.00	Ref	
	Overweight	46	1.28	0.62	2.67
	Obese	62	1.32	0.64	2.72
Smoker	Never	52	1.00	Ref	
	Current	18	2.33	1.32	4.12
	Former	34	1.01	0.64	1.58
Used respirator	No	15	1.00	Ref	
	Yes	99	0.95	0.51	1.78

aHR=adjusted hazard ratios, CI=confidence interval, LL=lower limit, UL=Upper limit

*Adjusted to all other variables in the table and to PTSD (yes/no)

**Insufficient sample size

*** Also shown in Figure 2

#See Table 1 for definitions

Table S3: Hazard ratios of incident (including recurrent) MI, recognized cardiovascular risk factors, and WTC exposure in 4942 men and 1029 women comprising WTC-Heart, New York, 2012-2016.

Gender		Categories#	No of MI	aHR*	95% CI	
					LL	UL
Men	All		61			
	Blood Pressure	Normal	41	1.00	ref	
		High	19	1.13	0.60	2.12
	Total cholesterol	Normal	50	1.00	ref	
		High	11	1.72	0.83	3.55
	BMI	Normal	6	1.00	ref	
		Overweight	23	0.97	0.36	2.60
		Obese	32	0.98	0.37	2.58
	Smoker	Never	22	1.00	ref	
		Current	11	3.34	1.55	7.18
		Former	20	1.36	0.72	2.58
	Used respirator	No	9	1.00	ref	
		Yes	50	0.97	0.38	2.45

Women	All		9			
	Blood Pressure	Normal	7	—**	—	
		High	2	—	—	
	Total cholesterol	Normal	8	—	—	
		High	1	—	—	
	BMI	Normal	0	—	—	
		Overweight	5	—	—	
		Obese	4	—	—	
	Smoker	Never	5	—	—	
		Current	0	—	—	
		Former	2	—	—	
	Used respirator	No	2	—	—	
		Yes	6	—	—	
All	All		69			
	Blood Pressure	Normal	48	1.00	ref	
		High	21	1.10	0.60	2.02

Total cholesterol	Normal	58	1.00	Ref	
	High	12	1.56	0.78	3.09
BMI	Normal	6	1.00	ref	
	Overweight	28	1.44	0.54	3.82
	Obese	36	1.37	0.52	3.64
Smoker	Never	27	1.00	Ref	
	Current	11	2.82	1.35	5.91
	Former	22	1.28	0.71	2.30
Used respirator	No	11	1.00	Ref	
	Yes	56	0.81	0.37	1.80

aHR=adjusted hazard ratios, CI=confidence interval, LL=lower limit, UL=Upper limit

*Adjusted to all other variables in the table and to PTSD (yes/no)

**Insufficient sample size

#See Table 1 for definitions

Table S4: Hazard ratios of incident (including recurrent) stroke, recognized cardiovascular risk factors, and WTC exposure in 4,942 men and 1,029 women comprising WTC-Heart, New York, 2012-2016.

Gender		Categories#	No of Stroke	aHR*	95% CI	
					LL	UL
Men	N		46			
	Blood Pressure	Normal	33	1.00	Ref	
		High	12	1.13	0.57	2.23
	Total cholesterol	Normal	42	1.00	Ref	
		High	4	0.84	0.30	2.36
	BMI	Normal	4	1.00	Ref	
		Overweight	17	1.22	0.35	4.21
		Obese	25	1.55	0.46	5.19
	Smoker	Never	24	1.00	Ref	
		Current	6	1.87	0.76	4.63
		Former	13	0.73	0.36	1.49
	Used respirator	No	6	1.00	Ref	
		Yes	40	0.82	0.32	2.08

Women	N		7			
	Blood Pressure	Normal	5	—**	—	
		High	2	—	—	
	Total cholesterol	Normal	7	—	—	
		High	0	—	—	
	BMI	Normal	1	—	—	
		Overweight	3	—	—	
		Obese	3	—	—	
	Smoker	Never	3	—	—	
		Current	1	—	—	
		Former	1	—	—	
	Used respirator	No	0	—	—	
		Yes	6	—	—	
All	N		53			
	Blood Pressure	Normal	38	1.00	Ref	
		High	14	1.30	0.68	2.67

Total cholesterol	Normal	49	1.00	Ref	
	High	4	0.73	0.26	2.03
BMI	Normal	5	1.00	Ref	
	Overweight	20	1.18	0.39	3.54
	Obese	28	1.39	0.47	4.06
Smoker	Never	27	1.00	Ref	
	Current	7	1.72	0.70	4.20
	Former	14	0.72	0.38	2.42
Used respirator	No	6	1.00	Ref	
	Yes	46	0.95	0.40	4.61

aHR=adjusted hazard ratios, CI=confidence interval, LL=lower limit, UL=Upper limit

*Adjusted to all other variables in the table and to PTSD (yes/no)

**Insufficient sample size

#See Table 1 for definitions

Table S5: Hazard ratios of exposure to the WTC complex cloud and incident (including recurrent) MI or stroke in 4942 men and 1029 women comprising WTC-Heart, New York, 2012-2016.

Exposure	Category	aHR*	LL	UL
Lower Manhattan	Yes	1.08	0.59	1.95
	No	1.00		
Directly in the cloud	Yes	0.76	0.32	1.88
	No	1.00		
Worked on the pile	Yes	1.30	0.69	2.46
	No	1.00		
First Day	9/11/2001 + cloud	1.00		
	9/11/2001 not on cloud	1.45	0.59	3.57
	9/12-13/2001	1.05	0.43	2.54
	9/14-30/2001	0.90	0.34	2.43
Summary Exposure	Low	1.00		
	Intermediate	1.21	0.57	2.54
	High	0.88	0.29	2.65

aHR=adjusted hazard ratios, CI=confidence interval, LL=lower limit, UL=Upper limit

*Adjusted for age and all variables shown in Table S3 and for PTSD

Table S6: Hazard ratios of probable PTSD and incident (including recurrent) MI

or stroke in 4942 men and 1029 women comprising WTC-Heart, New York, 2012-2016.

Analysis using Firth's correction.

Gender	Outcome	Measure	PTSD		Age-adjusted			Multivariate*		
			yes	No	HR	95% CI		HR	95% CI	
			Cases			LL	UL		LL	UL
Men	MI	Incident	23	38	2.29	1.36	3.85	2.22	1.25	3.94
	Stroke	Incident	19	27	2.71	1.25	3.94	2.76	1.48	5.13
	MI or Stroke	Incident	41	61	2.55	1.71	3.79	2.46	1.60	3.78
Women	MI	Incident	4	5	2.03	0.54	7.20	--**	--	--
	Stroke	Incident	3	4	2.11	0.47	8.75	--	--	--
	MI or Stroke	Incident	7	9	2.04	0.75	5.33	--	--	--
All	MI	Incident	27	43	2.24	1.38	3.64	2.22	1.30	3.82
	Stroke	Incident	22	31	2.61	1.51	4.53	2.51	1.39	4.57
	MI or Stroke	Incident	48	70	2.46	1.70	3.56	2.35	1.57	3.52

HR=hazard ratios, CI=confidence interval, LL=lower limit, UL=Upper limit

*Adjusted for age and all variables shown in Table S3

**Insufficient sample size

Table S7: Hazard ratios of PTSD and hospitalization for MI or stroke in 4533 men

and 951 women residing in New York City or State. WTC-Heart, 2012-2016.

Gender	Outcome	Measure	PTSD		Age-adjusted			Multivariate*		
			yes	No	HR	95% CI		HR	95% CI	
			Cases			LL	UL		LL	UL
Men	MI	Hospitalization	39	63	2.27	1.45	3.56	2.27	1.45	3.56
	Stroke	Hospitalization	29	36	2.97	1.82	4.87	3.12	1.81	5.41
	MI or Stroke	Hospitalization	64	94	2.45	1.78	3.37	2.65	1.87	3.76
Women	MI	Hospitalization	5	5	2.49	0.73	8.45	--	--	--
	Stroke	Hospitalization	5	7	1.97	0.61	5.95	--	--	--
	MI or Stroke	Hospitalization	10	12	2.44	1.05	5.55	--	--	--
All	MI	Hospitalization	44	68	2.20	1.50	3.20	2.17	1.41	3.32
	Stroke	Hospitalization	34	43	2.75	1.75	4.33	3.01	1.84	4.93
	MI or Stroke	Hospitalization	74	106	2.35	1.75	3.17	2.40	1.73	3.34

HR=hazard ratios, CI=confidence interval, LL=lower limit, UL=Upper limit

*Adjusted for age and all variables shown in Table S4

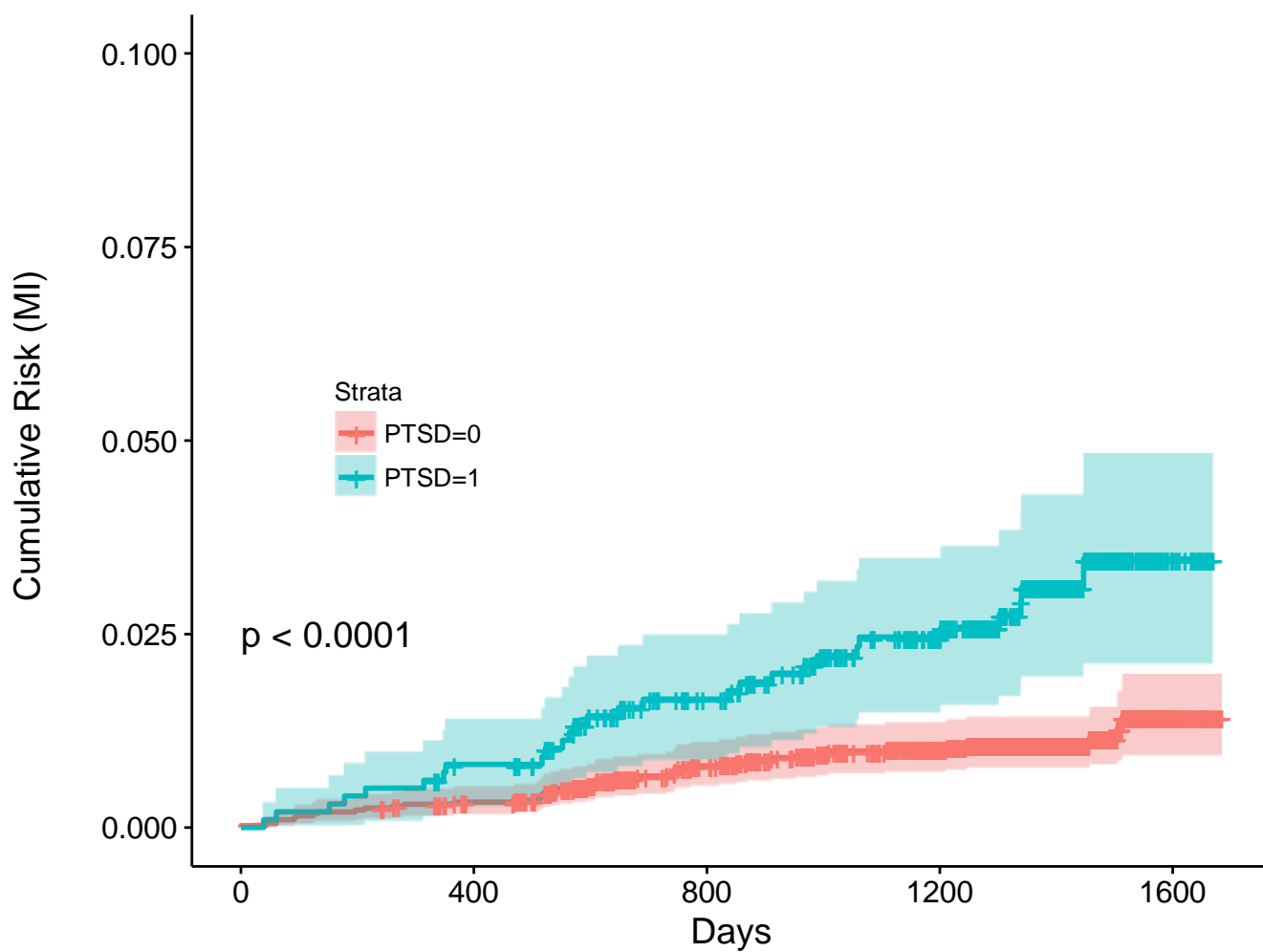
**Insufficient sample size

Table S8: Recognized cardiovascular risk factors and WTC exposure among 4942 men and 1029 women followed up and 424 men and 86 women lost to follow-up. WTC-Heart, New York, 2012-2016.

Gender		Categories#	% followed up out of n=4942	% lost out of n=424	p
Men	Blood Pressure	Normal	77.1	73.7	
		High	22.9	22.3	
	Total cholesterol	Normal	89.5	88.7	
		High	10.5	11.3	
	BMI	Normal	9.3	10.9	
		Overweight	40.7	35.4	
		Obese	50.0	53.8	
	Smoker	Never	60.8	57.0	
		Current	7.9	13.4	
		Former	31.3	29.7	
	Used respirator	No	10.5	10.4	
		Yes	89.5	89.6	
	PTSD	No	80.1	73.4	

	Yes	19.9	26.7	.001
Women		% followed up out of n=1029	% lost out of n=86	
Blood Pressure	Normal	87.4	80.9	
	High	12.6	19.1	.095
Total cholesterol	Normal	85.8	87.2	
	High	14.2	12.8	.720
BMI	Normal	25.1	18.6	
	Overweight	37.1	30.2	
	Obese	37.8	51.2	.049
Smoker	Never	66.8	69.1	
	Current	7.0	3.7	
	Former	26.2	27.2	.526
Used respirator	No	18.0	21.4	
	Yes	82.0	78.6	.434
PTSD	No	74.2	64.0	
	Yes	25.9	36.1	.040

All***		% followed up out of n=5971	% lost out of n=510	
Blood Pressure	Normal	78.9	75.0	
	High	21.1	25.0	.048
Total cholesterol	Normal	88.9	88.4	
	High	11.1	11.6	.749
BMI	Normal	12.0	12.2	
	Overweight	40.1	34.5	
	Obese	47.9	53.3	.038
Smoker	Never	61.8	59.1	
	Current	7.8	11.7	
	Former	30.4	29.2	.013
Used respirator	No	11.8	12.3	
	Yes	88.2	87.7	.752
PTSD	No	79.1	71.8	
	Yes	20.9	28.2	.000



Number of men at risk by time

Strata	0	400	800	1200	1600
PTSD=0	3952	3914	3720	3396	114
PTSD=1	980	968	895	772	44

Days

Figure S1: Cumulative risk of incident (including recurrent) myocardial infarction (MI) by PTSD status in men of the WTC-Heart cohort, New York, 2012-2016.

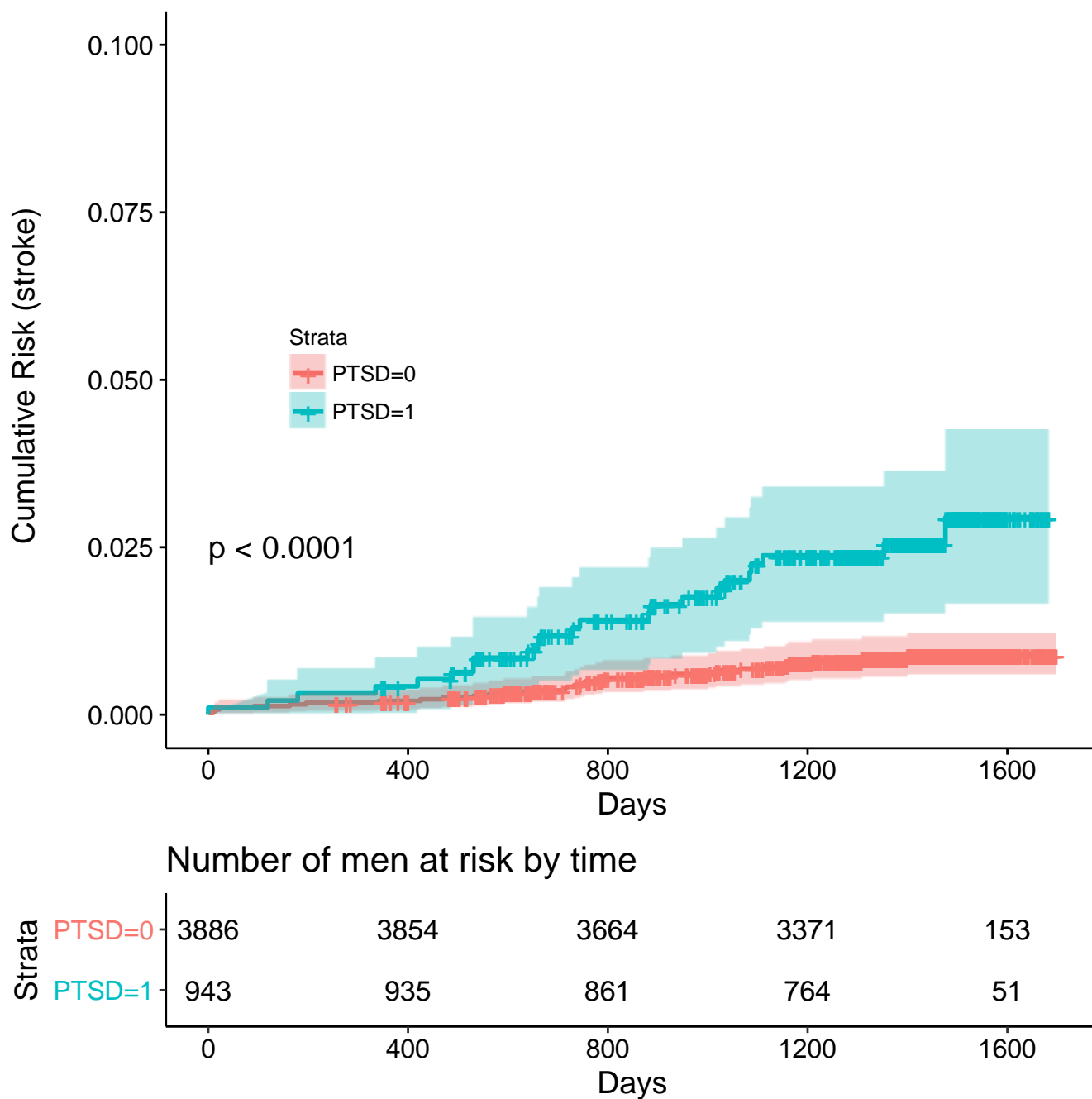
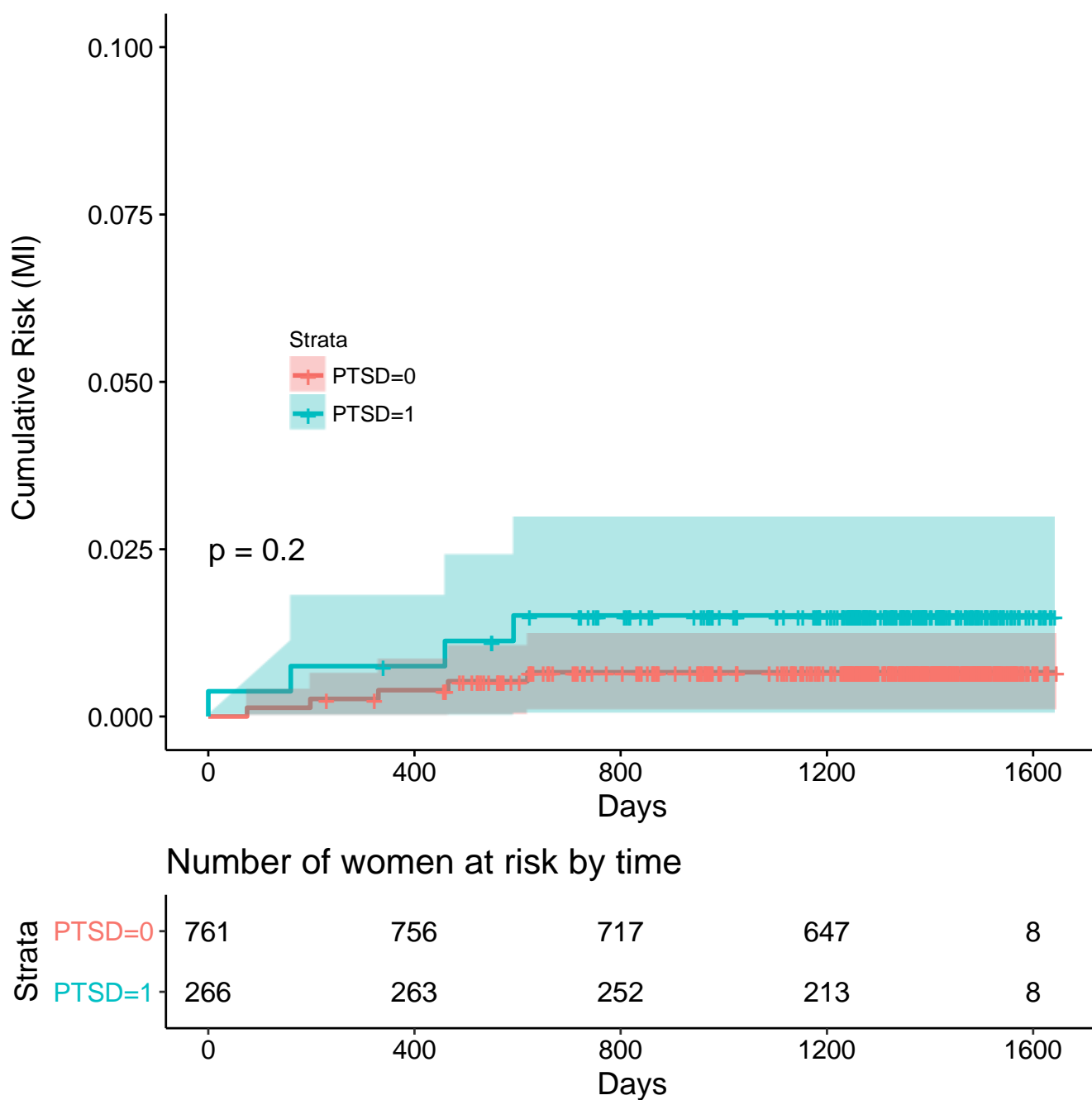


Figure S2: Cumulative risk of incident (including recurrent) stroke by PTSD status in the WTC-Heart cohort men, New York, 2012-2016.



Figure

S3: Cumulative risk of incident (including recurrent) myocardial infarction (MI) by PTSD status in women of the WTC-Heart cohort, New York, 2012-2016.

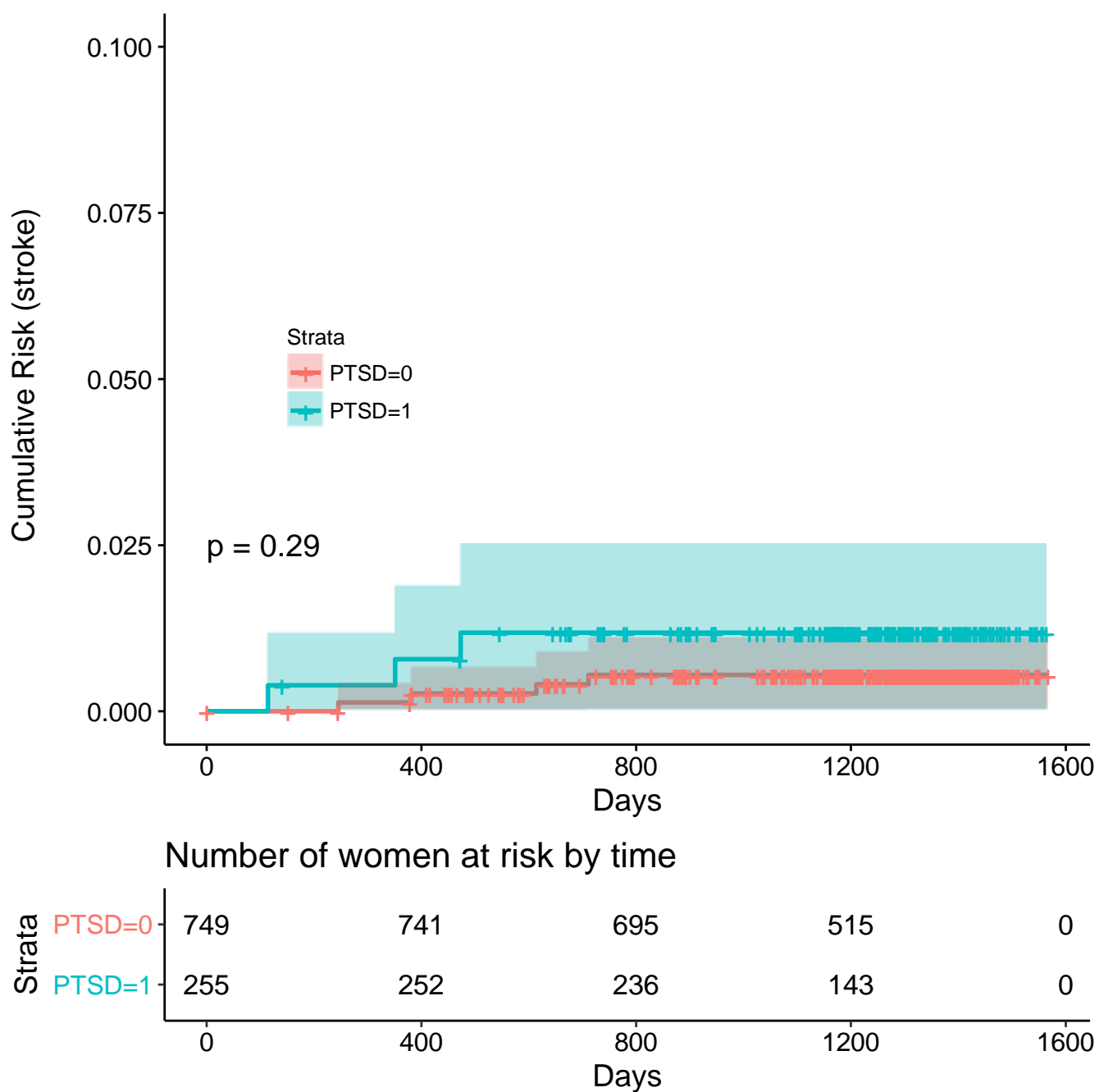


Figure S4: Cumulative risk of incident (including recurrent) stroke by PTSD status in the WTC-Heart cohort women, New York, 2012-2016.