Associations between stress disorders and cardiovascular disease events in the Danish population

Jaimie L Gradus,1,2,3 Dóra Körmeniné Farkas,3 Elisabeth Svensson,3 Vera Ehrenstein,3 Timothy L Lash,3,4 Arnold Milstein,5 Nancy Adler,6 Henrik Toft Sørensen3

ABSTRACT

Objectives: Post-traumatic stress disorder (PTSD) is a well-documented risk factor for cardiovascular disease (CVD). However, it is unknown whether another common stress disorder—adjustment disorder—is also associated with an increased risk of CVD and whether gender modifies these associations. The aim of this study was to examine the overall and gender-stratified associations between PTSD and adjustment disorder and 4 CVD events.

Design: Prospective cohort study utilising Danish national registry data.

Setting: The general population of Denmark.

Participants: PTSD (n=4724) and adjustment disorder (n=64 855) cohorts compared with the general population of Denmark from 1995 to 2011.

Primary outcome measures: CVD events including myocardial infarction (MI), stroke, ischaemic stroke and venous thromboembolism (VTE). Standardised incidence rates and 95% CIs were calculated.

Results: Associations were found between PTSD and all 4 CVD events ranging from 1.5 (95% CI 1.1 to 1.9) for MI to 2.1 (95% CI 1.7 to 2.7) for VTE. Associations that were similar in magnitude were also found for adjustment disorder and all 4 CVD events: 1.5 (95% CI 1.4 to 1.6) for MI to 1.9 (95% CI 1.8 to 2.0) for VTE. No gender differences were noted.

Conclusions: By expanding beyond PTSD and examining a second stress disorder—adjustment disorder—this study provides evidence that stress-related psychopathology is associated with CVD events. Further, limited evidence of gender differences in associations for either of the stress disorders and CVD was found.

Strengths and limitations of this study

First nationwide cohort study to examine post-traumatic stress disorder (PTSD) and adjustment disorder as risk factors for these four cardiovascular disease (CVD) events.

A substantial follow-up period and no selection bias.

Owing to sparse sample sizes, we were unable to examine precisely the associations between PTSD and all CVD events among those with comorbid depression or alcohol abuse diagnoses.

We were unable to adjust for behavioural risk factors for CVD events, such as smoking, which may have an impact on observed associations.

Post-traumatic stress disorder (PTSD), a diagnosis given following a traumatic event and in the presence of chronic trauma-related symptomatology, has been consistently shown to be associated with cardiovascular disease (CVD) in predominantly male samples of US Veterans and in the general population.6,7 Observed associations have been generally moderate in strength across studies. Veterans with PTSD have a 30–50% increased rate of incident myocardial infarction (MI) and heart failure than Veterans without PTSD.1,2,4,5 Among twin Veterans, those with PTSD have 2.2 the odds of CVD than those without PTSD.3 In the general population, people diagnosed with PTSD have 3.4 times the odds of heart failure than those without a PTSD diagnosis.8 Following the 11 September 2001 attacks, those who developed PTSD had 1.7 times the risk of CVD than those without PTSD.7

Despite this strong evidence of an association between PTSD and CVD, we know of no studies that have examined associations between a stress disorder diagnosis other than PTSD and CVD. One such diagnosis is adjustment disorder, which is a diagnosis given in the presence of chronic depressive or anxious symptomatology following a stressful life event (if diagnostic criteria for depression or anxiety disorders are not present).3,9 Although both disorders are linked to a precipitating stress event, they differ in the nature of the stress event and in the psychological responses. A study of the
The association between adjustment disorder and CVD could make an important contribution to the literature, as adjustment disorder is known to be a common, yet understudied, diagnosis both in the USA and abroad. Further, if adjustment disorder shows a comparable association with CVD than that of PTSD, it would provide support for the general impact of stress-related psychopathology on CVD.

The extant literature is also limited in assessing whether the association between stress disorders and CVD differs by gender. Gender-based examinations of risk factors for CVD are important; CVD is less common at older ages and develops later among women than men; however, CVD prognosis among women is comparable to or worse than that of men once diagnosed. Few studies have examined the association between PTSD and CVD among women explicitly. These studies have found evidence of a potentially strong association between adjustment disorder and CVD among women, but additional population-based longitudinal examinations of this association among women are needed to corroborate these findings. We know of no study that has examined gender differences in the association between adjustment disorders and CVD.

Given these gaps in the existing literature, the goal of the current study is to examine PTSD and adjustment disorders as risk factors for four CVD events (ie, MI, stroke, ischaemic stroke, and venous thromboembolism (VTE)) in a nationwide prospective cohort, both overall and stratified by gender.

METHODS
We used the Danish national registries to conduct a cohort study comparing the rate of four CVD events among patients with recorded PTSD or adjustment disorder diagnoses with the rate of expected diagnoses among the general population during the same period. The base population included residents of Denmark (Danish-born) from 1 January 1995 to 31 December 2011. Table 1 displays the characteristics of members of the PTSD and adjustment disorder cohorts.

Data sources
The Danish Civil Registration System (CRS) contains a unique identifier (the central personal registry (CPR) number), date of birth, gender and additional demographic data for all persons residing in Denmark since 1968. The CRS contains data on vital status for each resident and is updated daily. The CPR number can be used to link data across all Danish administrative and medical registries.

The Danish Psychiatric Central Research Registry (DPCRR) has collected data on inpatient and outpatient psychiatric treatment since 1995. It contains treatment dates and up to 20 diagnoses per treatment episode. We used the DPCRR to create a cohort of Danish residents with at least one incident International Classification of Diseases (ICD)-10 diagnosis of severe stress or adjustment disorder from 1 January 1995 to 31 December 2011. Patients with PTSD or adjustment disorder diagnoses (see online supplementary appendix 1 for ICD-10 codes) within that cohort were used for the current study. Any patients who were given both diagnoses on the same day were included in the group that corresponded with their primary diagnosis in the registry. Validation studies of diagnoses in the DPCRR (eg, schizophrenia and affective disorders) have been measured against computer-generated diagnoses or independent reinterviews, and these have shown high validity, including PTSD and adjustment disorder diagnoses contained within the DPCRR. We also used this registry to obtain data on depression and alcohol abuse, and dependence diagnoses for the stratified analyses.

The Danish National Patient Registry (DNPR) covers all inpatient non-psychiatric hospital treatment in Denmark since 1977, and outpatient and emergency room visits since 1995. The DNPR was used to identify patients with any of four CVD events, including MI, stroke, ischaemic stroke, and VTE. We also used data from the DNPR to compute a Charlson Comorbidity Index (CCI) score for each patient in our study as a measure of overall physical health status. Patients with PTSD and/or adjustment disorder diagnoses in the DNPR also were included in the current study.

Analyses
We calculated the expected number of incident CVD events after PTSD or adjustment disorder diagnoses separately using national incidence rates (restricted also to the Danish-born population of Denmark) of CVD events according to sex, 5-year age groups and 5-year calendar

Table 1 Characteristics of the PTSD and adjustment disorder cohorts, Denmark, 1995 to 2011

|                          | PTSD (n, %) | Adjustment Disorder (n, %) |
|--------------------------|------------|----------------------------|
|                          | (N=4724)   | (N=64 855)                 |
| Gender                   |            |                            |
| Male                     | 1867 (39.5)| 24 778 (38.2)              |
| Female                   | 2857 (60.5)| 40 077 (61.8)              |
| Age at diagnosis (years) |            |                            |
| 16–39                    | 2487 (52.7)| 37 949 (58.5)              |
| 40–59                    | 1976 (41.8)| 20 782 (32.0)              |
| 60+                      | 261 (5.5)  | 6124 (9.4)                 |
| Depression               |            |                            |
| Yes                      | 245 (5.2)  | 3855 (5.9)                 |
| No                       | 4479 (94.8)| 61 000 (94.1)              |
| Alcohol abuse/dependence diagnoses | | |
| Yes                      | 172 (3.6)  | 3335 (5.1)                 |
| No                       | 4552 (96.4)| 61 520 (94.9)              |
| CCI score                |            |                            |
| 0                        | 4046 (85.7)| 54 369 (83.8)              |
| 1+                       | 678 (14.3) | 10 486 (16.2)              |

CCI, Charlson Comorbidity Index; PTSD, post-traumatic stress disorder.
results. All statistical analyses were conducted using SAS V9.2. The study was approved by the Danish Data Protection Agency (record number 2012-41-0841), and by the Institutional Review Board at Boston University.

RESULTS

Post-traumatic stress disorder

We identified 4724 adults with a diagnosis of PTSD who had never been diagnosed with a CVD event (60% female) before the start of the study period. Patients with PTSD were followed for an average of 7.9 years (median follow-up 7 years; range 1–18 years). Age at PTSD diagnosis ranged from 16 to 94 years (mean age 39.3 years; median age 39 years). Among patients with PTSD, 54 cases of MI, 95 cases of stroke, 50 cases of ischaemic stroke and 78 cases of VTE were diagnosed during the follow-up period.

Table 2 displays associations between PTSD and incidence of CVD events. We found moderate associations ranging from an SIR of 1.5 (95% CI 1.1 to 1.9) for MI, to 2.1 (95% CI 1.7 to 2.7) for VTE. Associations were generally consistent by sex, with the exception of ischaemic stroke, which had a stronger association with PTSD among males than females. Across CVD events, associations with PTSD were strongest in the youngest age group (16–39 years), with either no change or decreasing risk ratio from age 40 years onward. Stratified analyses further revealed that associations between PTSD

| CVD events | Myocardial infarction | Stroke | Ischaemic stroke | Venous thromboembolism |
|------------|------------------------|--------|-----------------|-------------------------|
|            | O E SIR (95% CI)       | O E SIR (95% CI) | O E SIR (95% CI) | O E SIR (95% CI)       |
| PTSD       |                        |        |                 |                         |
| Gender     |                        |        |                 |                         |
| Male       | 54 37.2 1.5 (1.1 to 1.9) | 95 55.0 1.7 (1.4 to 2.1) | 50 27.6 1.8 (1.4 to 2.4) | 78 36.7 2.1 (1.7 to 2.7) |
| Female     | 33 21.3 1.6 (1.1 to 2.2) | 43 24.0 1.8 (1.3 to 2.4) | 30 12.5 2.4 (1.6 to 3.4) | 30 13.3 2.3 (1.5 to 3.2) |
| Age at PTSD diagnosis (years) |        |        |                 |                         |
| 16–39      | 12 4.7 2.6 (1.3 to 4.5) | 23 7.6 3.0 (1.9 to 4.6) | 10 3.9 2.6 (1.2 to 4.8) | 31 12.0 2.6 (1.8 to 3.7) |
| 40–59      | 29 22.8 1.3 (0.85 to 1.8) | 53 30.9 1.7 (1.3 to 2.2) | 32 16.4 2.0 (1.3 to 2.8) | 36 19.0 1.9 (1.3 to 2.6) |
| 60+        | 13 9.7 1.3 (0.72 to 2.3) | 19 16.5 1.2 (0.69 to 1.8) | 8 7.3 1.1 (0.47 to 2.2) | 11 5.8 1.9 (0.95 to 3.4) |
| Depression diagnosis |        |        |                 |                         |
| Yes        | – – – | 8 3.5 2.3 (1.0 to 4.5) | – – – | – – – | – – – | – – – | – – – |
| No         | 51 34.9 1.5 (1.1 to 1.9) | 87 51.5 1.7 (1.4 to 2.1) | 47 25.8 1.8 (1.3 to 2.4) | 74 34.8 2.1 (1.7 to 2.7) |
| Alcohol diagnoses |        |        |                 |                         |
| Yes        | – – – | 5 1.8 2.8 (0.91 to 6.6) | – – – | – – – | – – – | – – – | – – – |
| No         | 52 35.7 1.5 (1.1 to 1.9) | 90 53.2 1.7 (1.4 to 2.1) | 48 26.6 1.8 (1.3 to 2.4) | 74 35.6 2.1 (1.6 to 2.6) |
| CCI score  |        |        |                 |                         |
| 0          | 38 30.6 1.2 (0.88 to 1.7) | 71 45.0 1.6 (1.2 to 2.0) | 39 22.6 1.7 (1.2 to 2.4) | 58 31.2 1.9 (1.4 to 2.4) |
| 1+         | 16 6.6 2.4 (1.4 to 3.9) | 24 10.0 2.4 (1.5 to 3.6) | 11 5.0 2.2 (1.1 to 4.0) | 20 5.5 3.6 (2.2 to 5.6) |
| Follow-up time (years) |        |        |                 |                         |
| 1 to <5    | 22 15.1 1.5 (0.91 to 2.2) | 40 22.0 1.8 (1.3 to 2.5) | 22 10.1 2.2 (1.4 to 3.3) | 27 14.5 1.9 (1.2 to 2.7) |
| 5 to <10   | 21 13.4 1.6 (0.97 to 2.4) | 33 19.7 1.7 (1.2 to 2.4) | 17 10.0 1.7 (0.99 to 2.7) | 30 13.1 2.3 (1.6 to 3.3) |
| 10+        | 11 8.6 1.3 (0.64 to 2.3) | 22 13.3 1.7 (1.0 to 2.5) | 11 7.5 1.5 (0.73 to 2.6) | 21 9.1 2.3 (1.4 to 3.5) |

Data for strata with less than five participants not presented.

CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; PTSD, post-traumatic stress disorder; SIR, standardised incidence rate.
and all four CVD events exist in the absence of depression and alcohol abuse and dependence diagnoses. For all CVD events, the associations with PTSD were present regardless of comorbidity status. No meaningful differences in the magnitude of effects across strata of follow-up time were observed.

We conducted a bias analysis to examine the potential impact of uncontrolled confounding due to smoking, a potentially strong confounder, on our observed associations between PTSD and CVD events. The prevalence of smoking among people with and without PTSD is well documented (~58.1% and ~39.1%, respectively) as is the approximately 2.5-fold risk of CVD among smokers. Using these parameters, we were able to estimate the potential bias in the observed PTSD and CVD event associations due to uncontrolled confounding by smoking. This analysis revealed a ratio of 1.18 for the unadjusted PTSD and CVD ORs, which indicates that uncontrolled confounding due to smoking does not completely account for our observed associations between PTSD and CVD events, assuming a valid bias model.

Adjustment disorder

We identified 64,855 adults with a diagnosis of adjustment disorder who had never been diagnosed with a CVD event (62% female) prior to the study period. Patients with adjustment disorder were followed for an average of 8.2 years (median follow-up 7.6 years; range 1–18 years). Age at adjustment disorder diagnosis ranged from 16 to 97 years (mean age 38.3 years; median age 36.2 years). Among patients with adjustment disorder, 803 cases of MI, 1483 cases of stroke, 712 cases of ischaemic stroke and 1006 cases of VTE were diagnosed during the follow-up period.

The associations between adjustment disorder and CVD events are displayed in table 3. Similar to our results for PTSD, we found moderate associations for adjustment disorder and the four CVD events ranging from an SIR of 1.5 (95% CI 1.4 to 1.6) for MI to 1.9 (95% CI 1.8 to 2.0) for VTE. Associations were generally consistent across all CVD events. Associations between adjustment disorder and the four CVD events were strongest in the youngest age group (16–39 years), with decreasing risk ratios from age 40 years onward. Results from across the strata of depression diagnosis, alcohol abuse and dependence diagnoses, and comorbidity revealed associations among those with and without these potential confounders. The magnitude of associations was similar across stratified analyses that examined different periods of follow-up time.

DISCUSSION

This is the first nationwide cohort study to examine PTSD and adjustment disorder as risk factors for four CVD events. Our results are consistent with the body of research that supports PTSD as a risk factor for CVD in various groups. The current study expands on this previous work in two important ways. First, we examined a second chronic severe stress disorder, adjustment disorder, and found that its associations with CVD events were similar in magnitude to those for PTSD. Both PTSD and adjustment disorder represent potentially important risk factors for CVD. Mechanisms through which stress disorders and CVD events may be associated include increased inflammation, increased allostatic load, dysregulation of the hypothalamic–pituitary–adrenal axis, autonomic nervous system dysfunction, behavioural risk factors (eg, substance abuse, smoking), shared genetic risk factors, metabolic syndrome and depression. Interestingly, the observed number of stroke and ischaemic stroke events in this sample was high given the expected observation and the age range of the sample. This may be explained by hypertension which is associated with stress disorders and a well-known risk factor for stroke. We explored this possibility via stratified analysis, and found that the association between PTSD and stroke was attenuated among people with incident hypertension following their stress diagnosis (SIR=1.0, 95% CI 1.3 to 2.1); however, the association between adjustment disorder and stroke was not (SIR=3.2, 95% CI 2.7 to 3.7). Understanding the mechanisms that underlie the association between adjustment disorder and stroke is an important area for future research. While the evidence of mechanistic links between stress and MI is strong, less is known about the mechanisms for associations between stress and stroke or VTE. Given the comparable association magnitudes, we observed for all CVD events in the current study, the well-documented mechanisms that underlie the stress and MI association may play a similar role in the association between stress disorders and other CVD events. Future mechanistic studies should explore these possibilities.

A second expansion on the literature provided by the current study is the ability to examine the associations between stress disorders and CVD events separately by gender. Previous research has been limited by small numbers of women, and examinations of gender as a modifier of this association have been few.

With the exception of ischaemic stroke, which was observed to be more strongly related to PTSD and to adjustment disorder among men than among women, we found that associations between events and either PTSD or adjustment disorder were similar in magnitude across gender. Since previous studies have not found gender differences in risk of stroke, the gender difference we have noted may be an important area for future research. In other stratified analyses, we found associations between the two stress disorders and CVD events among patients with and without depression and alcohol abuse and dependence diagnoses, and among patients with any CCI score indicating that these associations exist independent of depression, alcohol abuse and dependence or physical comorbidity status.

Gradus JL, et al. BMJ Open 2015;5:e009334. doi:10.1136/bmjopen-2015-009334

BMJ Open: first published as 10.1136/bmjopen-2015-009334 on 14 December 2015. Downloaded from http://bmjopen.bmj.com/ on September 24, 2023 by guest. Protected by copyright.
| CVD events | Myocardial infarction | Stroke | Ischaemic stroke | Venous thromboembolism |
|-----------|-----------------------|--------|-----------------|------------------------|
|           | O    | E    | SIR (95% CI)    | O    | E    | SIR (95% CI) | O    | E    | SIR (95% CI) |
| Adjustment disorder | 803  | 550.4 | 1.5 (1.4 to 1.6) | 1483 | 839.6 | 1.8 (1.7 to 1.9) | 712  | 409.8 | 1.7 (1.6 to 1.9) | 1006 | 537.0 | 1.9 (1.8 to 2.0) |
| Gender | | | | | | | | | |
| Male | 422  | 292.3 | 1.4 (1.3 to 1.6) | 614  | 333.2 | 1.8 (1.7 to 2.0) | 313  | 169.1 | 1.9 (1.7 to 2.1) | 373  | 181.6 | 2.1 (1.9 to 2.3) |
| Female | 381  | 258.1 | 1.5 (1.3 to 1.6) | 869  | 506.4 | 1.7 (1.6 to 1.8) | 399  | 240.7 | 1.7 (1.5 to 1.8) | 633  | 355.4 | 1.8 (1.7 to 1.9) |
| Age at adjustment disorder diagnosis (years) | | | | | | | | | |
| 16–39 | 156  | 76.5 | 2.1 (1.7 to 2.4) | 290  | 121.1 | 2.4 (2.1 to 2.7) | 139  | 61.5 | 2.3 (1.9 to 2.7) | 427  | 189.1 | 2.3 (2.1 to 2.5) |
| 40–59 | 386  | 260.3 | 1.5 (1.3 to 1.6) | 719  | 354.6 | 2.0 (1.9 to 2.2) | 370  | 184.4 | 2.0 (1.8 to 2.2) | 399  | 216.7 | 1.8 (1.7 to 2.0) |
| 60+ | 261  | 213.5 | 1.2 (1.1 to 1.4) | 474  | 363.9 | 1.3 (1.2 to 1.4) | 203  | 163.8 | 1.2 (1.1 to 1.4) | 180  | 131.2 | 1.4 (1.2 to 1.6) |
| Depression diagnoses | | | | | | | | | |
| Yes | 86  | 52.3 | 1.6 (1.3 to 2.0) | 161  | 84.6 | 1.9 (1.6 to 2.2) | 79  | 40.3 | 2.0 (1.6 to 2.4) | 90  | 41.4 | 2.2 (1.8 to 2.7) |
| No | 717  | 498.1 | 1.4 (1.3 to 1.6) | 1322 | 755.0 | 1.8 (1.7 to 1.9) | 633  | 369.5 | 1.7 (1.6 to 1.9) | 916  | 495.6 | 1.9 (1.7 to 2.0) |
| Alcohol diagnoses | | | | | | | | | |
| Yes | 66  | 35.6 | 1.9 (1.4 to 2.4) | 168  | 45.3 | 3.7 (3.2 to 4.3) | 80  | 23.4 | 3.4 (2.7 to 4.3) | 86  | 27.2 | 3.2 (2.5 to 3.9) |
| No | 737  | 514.8 | 1.4 (1.3 to 1.5) | 1315 | 794.3 | 1.7 (1.6 to 1.8) | 632  | 386.4 | 1.6 (1.5 to 1.8) | 920  | 509.8 | 1.8 (1.7 to 1.9) |
| CCI score | | | | | | | | | |
| 0 | 550  | 425.0 | 1.3 (1.2 to 1.4) | 1051 | 641.4 | 1.6 (1.6 to 1.7) | 512  | 316.0 | 1.6 (1.5 to 1.8) | 781  | 437.7 | 1.8 (1.7 to 1.9) |
| 1+ | 253  | 125.3 | 2.0 (1.8 to 2.3) | 432  | 198.2 | 2.2 (2.0 to 2.4) | 200  | 93.8 | 2.1 (1.9 to 2.5) | 225  | 99.2 | 2.3 (2.0 to 2.6) |
| Follow-up time (years) | | | | | | | | | |
| 1 to <5 | 297  | 218.3 | 1.4 (1.2 to 1.5) | 597  | 334.7 | 1.8 (1.6 to 1.9) | 271  | 146.2 | 1.9 (1.6 to 2.1) | 409  | 203.6 | 2.0 (1.8 to 2.2) |
| 5 to <10 | 308  | 196.5 | 1.6 (1.4 to 1.8) | 510  | 299.5 | 1.7 (1.6 to 1.9) | 232  | 146.4 | 1.6 (1.4 to 1.8) | 350  | 192.6 | 1.8 (1.6 to 2.0) |
| 10+ | 198  | 135.6 | 1.5 (1.3 to 1.7) | 376  | 205.5 | 1.8 (1.7 to 2.0) | 209  | 117.3 | 1.8 (1.6 to 2.0) | 247  | 140.7 | 1.8 (1.5 to 2.0) |

CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; SIR, standardised incidence rate.
Previous research found that the risk of MI and other cardiovascular events increase within weeks or months following a stressful or traumatic experience. Since we started our follow-up time for CVD events at 1 year following the stress diagnosis as a conservative measure to ensure that the stress diagnosis was not a result of the CVD event, our study did not include the time period in which increased associations between stress and CVD events have been observed previously. As a result, our findings may underestimate the magnitude of the impact of stress on CVD. We did not find differences in the magnitude of stress disorder and CVD associations by length of follow-up time, suggesting that the increased risk of CVD events following stress disorder diagnoses remains relatively consistent beginning at 1 through more than 10 years after diagnosis.

There are ways in which PTSD and adjustment disorder differ, which are important contextual information to consider in the interpretation of our findings. For example, chronicity differs between the two disorders, with PTSD being a longer duration disorder with no definitive end point and adjustment disorder limited to 6 months in duration. Given this, it is perhaps surprising that we did not observe a stronger association for PTSD and CVD events than we did for adjustment disorder. The similarity in strength of association could be because adjustment disorder may be used as a catch-all diagnosis for people who experience stressful events but do not meet full criteria for PTSD; if so, our adjustment disorder cohort may include people who have experienced a significant stressor and have subsyndromal PTSD. The finding of comparable associations for PTSD and adjustment disorder with CVD may also reflect the larger overlap between adjustment disorder and depression symptomatology than between PTSD and depression symptomatology. Depression is a known risk factor for CVD, while our analyses adjust for depression diagnosis and suggest that it does not influence our observed associations, we only adjusted for baseline depression diagnosis and did not assess the potentially additional role of chronic depression.

Criticisms of the adjustment disorder diagnosis should be considered when interpreting our results. The diagnosis has been criticised for being unreliable and including people with a variety of symptomatology and experiences which do not meet criteria for depressive, anxiety or other disorders. However, a validation study of stress diagnoses in Denmark showed that both adjustment disorder and PTSD registry-based diagnoses had high validity when compared with chart review by an independent assessor. Despite this, those diagnosed with adjustment disorder in the current study may have experienced a wide range of stressors and poststress symptomatology severity that is representative of general distress.

Strengths of the current study include a large population-based cohort sample with a substantial follow-up period and no selection bias. Even with the large, well-characterised sample, some limitations must be kept in mind when interpreting our results. Owing to sparse subgroup sizes, we were unable to examine precisely the associations between PTSD and three of the CVD events among those with depression diagnoses. We were unable to adjust for behavioural risk factors for CVD events and other potentially important confounders, which may have biased observed associations. Importantly, the bias analysis we conducted to evaluate the potential impact of uncontrolled confounding due to smoking on the associations between PTSD and CVD events indicates that this uncontrolled confounding did not account for our entire observed association. Data from the DNPR are frequently used for the study of CVD events, however, validation studies comparing stroke and TVE diagnoses obtained from the DNPR with medical records have found the positive predictive value of the diagnoses contained in the registry to be moderate and variable across diagnostic subgroups, treatment departments (eg, emergency room, specialty department) and type of diagnosis (primary vs secondary). It is also important to note that data from this study were obtained from administrative treatment registries. Although it is estimated that 99% of the Danish population makes contact with the healthcare system in a given year, the sample for the current study consisted of treatment-seeking patients and hence, may not be representative of segments of the population who do not seek mental healthcare. Finally, it is important to note that the size of SIRs across PTSD and adjustment disorder exposure groups may not be directly comparable because these have been standardised to slightly different populations; however, the current study is consistent with circumstances under which these differences would not have a meaningful impact on observed associations.

In conclusion, this study provides evidence of associations between PTSD and adjustment disorder diagnoses and four CVD events, both on the overall and by gender. Future research utilising population-based samples is needed to further elucidate the mechanisms that underlie the associations between stress diagnoses and CVD events.

Author affiliations
1National Center for PTSD, VA Boston Healthcare System, Boston, Massachusetts, USA
2Departments of Psychiatry and Epidemiology, Boston University, Boston, Massachusetts, USA
3Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
4Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA
5Clinical Excellence Research Center, Stanford University, Stanford, California, USA
6Department of Psychiatry, University of California, San Francisco, California, USA

Contributors All authors made substantial contributions to the design of the study, and interpretation of the data. DKF and ES made substantial contributions to the acquisition and analysis of data. All authors contributed
REFERENCES

1. Kubzansky LD, Koenen KC, Spiro A, et al. Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the Normative Aging Study. Arch Gen Psychiatry 2007;64:109–16.

2. Scherrer JP, Chruściel T, Zeringue A, et al. Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans administration patients. Am J Heart 2010;159:722–9.

3. Vaccarino V, Goldberg J, Rooks C, et al. Post-traumatic stress disorder and incidence of coronary heart disease. J Am Coll Cardiol 2013;62:970–8.

4. Bilirianos MH, Yaffe K, Cohen B, et al. PTSD and cardiovascular disease. J Geriat Psychiatry 2014, in press.

5. Roy SS, Foraker RE, Girton RA, et al. Posttraumatic stress disorder and incident heart failure among a community-based sample of US veterans. Am J Public Health 2015;105:757–63.

6. Spitzer C, Barnow S, Volzke H, et al. Posttraumatic stress disorder, and physical illness: findings from the general population. Scand J Public Health 2015;43:106–15.

7. Jordan HT, Miller-Archie SA, Cone JE, et al. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. Am J Heart 2013;66:806–14.

8. Schmidt M, Jacobsen JB, Lash TL, et al. The Danish Civil Registration System: a tool in epidemiology. Eur J Epidemiol 2014;29:541–9.

9. Munk-Jorgensen P, Mortensen PB, The Danish Psychiatric Central Register. Dan Med Bull 1997;44:82–4.

10. Mors O, Perto GP, Mortensen P, The Danish Psychiatric Central Register. Scand J Public Health 2011;39:54–7.

11. Svensson E, Lash TL, Resick PA, et al. Validity of reaction to severe stress and adjustment disorders diagnoses in the Danish Psychiatric Central Registry. Clin Epidemiol 2015;7:235–42.

12. Lyne E, Sandegaard JL, Reboli M, The Danish National Patient Register. Scand J Public Health 2011;39:30–3.

13. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

14. Rothman KJ, Boice JD. Epidemiologic analyses with a programmable calculator. Washington DC: Government Printing Office, 1979.

15. Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness: a population-based prevalence study. JAMA 2000;284:2606–10.

16. Burns DM. Epidemiology of smoking-induced cardiovascular disease. Prog Cardiovasc Dis 2003;46:11–28.

17. Greenblatt A, Lash TL. Bias analysis. In: Rothman KJ, Greenland S, Lash TL, eds. Modern epidemiology, 3rd edn. Philadelphia, PA: Lippincott, Williams & Wilkins, 2008:345–80.

18. Edmondson D, Cohen B. Posttraumatic stress disorder and cardiovascular disease. Prog Cardiovasc Dis 2013;55:548–56.

19. Coughlin SS. Post-traumatic stress disorder and cardiovascular disease. Open Cardiovasc Med J 2011;5:164–70.

20. Boscano JA. Post-traumatic stress disorder and cardiovascular disease link: time to identify specific pathways and interventions. Am J Cardiol 2011;108:1052–3.

21. Wentworth BA, Stein MB, Redwine LS, et al. Post-traumatic stress disorder: a fast track to premature cardiovascular disease? Cardiol Rev 2013;21:16–25.

22. Bedi US, Arora R. Cardiovascular manifestations of posttraumatic stress disorder. J Natl Med Assoc 2007;99:642–9.

23. Dedert EA, Calhoun PS, Watkins LL, et al. Posttraumatic stress disorder, cardiovascular and metabolic disease: a review of the evidence. Ann Behav Med 2010;39:61–7.

24. McFarlane AC. The long-term costs of traumatic stress: intertwined physical and psychological consequences. World Psychiatry 2010;9:3–10.

25. Poullier NR, Prabhakaran D, Caulfield M. Hypertension. Lancet 2015;386:801–12.

26. Stepne A, Kivimaki M. Stress and cardiovascular disease. Nat Rev Cardiol 2012;9:360–70.

27. Schulz UGR, Rothwell PM. Differences in vascular risk factors between etiologic subtypes of ischemic stroke: importance of population-based studies. Stroke 2003;34:2050–9.

28. Nawrot TS, Perez L, Kunzli N, et al. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet 2011;377:732–40.

29. Mittelman MA, Mostofsky E. Physical, psychological and chemical triggers of acute cardiovascular events: preventative strategies. Circulation 2011;124:346–54.

30. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease. JAMA Psychiatry 1998;55:890–2.

31. Svensson E, Antonsson S, Lash TL, et al. Validity of reaction to severe stress and adjustment disorders diagnoses in the Danish Psychiatric Central Registry. Clin Epidemiol 2014;7:235–42.

32. Schmidt M, Hovath-Puho E, Christiansen CF, et al. Preadmission use of nonsteroidal anti-inflammatory drugs and 30-day stroke mortality. Neurology 2014;83:2013–22.

33. Sorensen HT, Hovath-Puho E, Lash TL, et al. Heart disease may be a risk factor for pulmonary embolism without peripheral deep venous thrombosis. Circulation 2011;124:1435–41.

34. Johnsen SP, Overvad K, Jensen RF, et al. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. J Clin Epidemiol 2002;55:602–7.

35. Severinsen MT, Kristensen SR, Overvad K, et al. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. J Clin Epidemiol 2010;63:223–8.

36. Statistics Denmark. Visit to a doctor etc. 2010. http://www.dst.dk/ homeuk/Stats/bb focus on/focus on show.aspx?sci=1316

37. Greenland S, Rothman KJ, Lash TL. Measures of effect and measures of association. In: Rothman KJ, Greenland S, Lash TL, eds. Modern epidemiology, 3rd edn. Philadelphia, PA: Lippincott, Williams & Wilkins, 2008:51–70.