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

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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[1–5] 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.[6] 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).[8] 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

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.[9] [10] 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.[11] 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.[12] [13] Few studies have examined the association between PTSD and CVD among women explicitly.[7] [14–16] These studies have found evidence of a potentially strong association between PTSD 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.[17] 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.[18] [19] 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

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

	PTSD (n, %) (N=4724)	Adjustment Disorder (n, %) (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.

Classification of Diseases (ICD)-10 diagnosis of severe stress or adjustment disorder from 1 January 1995 to 31 December 2011.[9] 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,[18] [19] including PTSD and adjustment disorder diagnoses contained within the DPCRR.[20] 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.[21] 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.[22] 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

periods. Multiplying person-years of follow-up and incidence rates yielded the number of CVD events that would be expected if those with PTSD or adjustment disorder diagnoses had the same CVD event risk as the general population.[23] We calculated standardised incidence ratios (SIRs) to measure the association between PTSD or adjustment disorder and CVD events, as the ratio of observed to expected cases. CIs were calculated assuming that the observed number of CVD events followed a Poisson distribution. Exact confidence limits were calculated when there were fewer than 10 observed CVD events; Byar's approximation was used otherwise.[23] Presentation of stratified results is limited to CVD events with at least five incident cases among people with PTSD or adjustment disorder within each subgroup.

We restricted our analyses to CVD events diagnosed one or more years after the PTSD or adjustment disorder diagnosis date to ensure that the stress diagnosis was not subsequent to the CVD event diagnosis. We further restricted our analyses to adults, defined as age 16 years or older. Analyses were stratified by sex, age at stress diagnosis (16–39, 40–59, and 60+ years), depression and alcohol abuse and dependence diagnostic status at the start of the study period, CCI score, and time interval between first stress diagnosis and incident CVD event diagnosis (1 to <5, 5 to <10 and 10+ years). Finally, we conducted a bias analysis for the association between PTSD and CVD events to examine the impact that uncontrolled confounding due to smoking would have on these

results. All statistical analyses were conducted using SAS V.9.2. 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

Table 2 Stratified associations between PTSD and CVD events, Denmark, 1995–2011

	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	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)
Gender												
Male	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)
Female	21	15.9	1.3 (0.82 to 2.0)	52	31.0	1.7 (1.3 to 2.2)	20	15.0	1.3 (0.81 to 2.1)	48	23.4	2.1 (1.5 to 2.7)
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),[24] as is the approximately 2.5-fold risk of CVD among smokers.[25] 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.[26] This analysis revealed a ratio of 1.18 for the unadjusted to adjusted 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 by sex across 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.[1–7] 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.[27–32] 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.[33 34] 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 2.10): 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,[35] 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.[11] Previous research has been limited by small numbers of women, and examinations of gender as a modifier of this association have been few.[7 14 15] 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,[36] 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.

Table 3 Stratified associations between adjustment disorder and CVD events, Denmark, 1995–2011

	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)**
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.[37 38] 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 understate 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.[8] 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[39]; 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.[10] 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.[40] 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;[12 41 42] however, validation studies comparing stroke and VTE 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).[43 44] 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;[45] 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.[46]

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.

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