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Original Contribution

Stress Disorders and Dementia in the Danish Population

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There is an association between stress and dementia. However, less is known about dementia among persons with varied stress responses and sex differences in these associations. We used this population-based cohort study to examine dementia among persons with a range of clinician-diagnosed stress disorders, as well as the interaction between stress disorders and sex in predicting dementia, in Denmark from 1995 to 2011. This study included Danes aged 40 years or older with a stress disorder diagnosis ($n = 47,047$) and a matched comparison cohort ($n = 232,141$) without a stress disorder diagnosis with data from 1995 through 2011. Diagnoses were culled from national registries. We used Cox proportional hazards regression to estimate associations between stress disorders and dementia. Risk of dementia was higher for persons with stress disorders than for persons without such diagnosis; adjusted hazard ratios ranged from 1.6 to 2.8. There was evidence of an interaction between sex and stress disorders in predicting dementia, with a higher rate of dementia among men with stress disorders except posttraumatic stress disorder, for which women had a higher rate. Results support existing evidence of an association between stress and dementia. This study contributes novel information regarding dementia risk across a range of stress responses, and interactions between stress disorders and sex.

cohort study; dementia; stress disorders, traumatic

Abbreviations: CI, confidence interval; PTSD, posttraumatic stress disorder.

Stress disorders, particularly posttraumatic stress disorder (PTSD), occur frequently and are associated with significant costs to individuals and society ([1]). Similarly, dementia is an increasingly costly public health concern ([2]), with prevalence growing annually ([3]). Given the ubiquity of these conditions, a deeper understanding of their association could have a significant public health impact.

An association between stress and dementia has been documented across population-based studies ([4–9]). For example, self-reported experiences of everyday life stress during middle age were related to dementia diagnosis in a longitudinal population-based study of women in Gothenburg, Sweden ([4]). Work-related stress was associated with dementia in a population-based sample of Swedish twins ([5]). In the United States, in a study based on longitudinal data from the Kaiser Permanente Northern California health system, PTSD was associated with a 2-fold increased risk of dementia in men and a 1.6-fold increase in women ([6]). In a predominantly male sample of

veterans using US Department of Veterans Affairs health care, veterans with PTSD had 1.7 times the rate of dementia of veterans without PTSD (95% confidence interval (CI): 1.7, 1.9) ([7]). A smaller study of US veterans compared risk of dementia among veterans with PTSD who had received a Purple Heart medal (awarded to US service members wounded in combat) with that among veterans without PTSD or a Purple Heart. Interestingly, a higher odds ratio of dementia was found among veterans who had a PTSD diagnosis but no Purple Heart compared with those who had neither (adjusted odds ratio = 2.3, 95% CI: 2.0, 2.7) ([8]). Dementia symptoms were also higher among persons aged 65 or older with major housing damage from the 2011 Great East Japan Earthquake and Tsunami ([9]).

Although most published studies on the subject have documented an association between stress and dementia, unanswered questions remain with regard to understanding of the association between dementia and a range of stress responses. Similarly, few studies have examined the gender differences in the association

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between stress and dementia in a single source of data. A recent review of stress and dementia called for well-designed longitudinal studies to further examine this association (10). Thus, the aim of the current study was to examine the risk of dementia among persons with stress disorders, which capture a wide range of stress reactions (including acute stress reaction, PTSD, adjustment disorder, and 2 unspecified stress diagnoses). Furthermore, we examined the interaction between stress disorders and sex in predicting the rate of dementia.

METHODS

Setting and design

The source population for this nationwide cohort study was the entire population of Denmark (approximately 3.59 million persons), between 1995 and 2011, aged 40 years or older. Denmark's many nationwide registries collectively contain diverse social and medical data, providing an optimal setting for population-wide epidemiologic research (11, 12). Data from all registries can be linked using a unique personal identifier (the central personal registry number) assigned to all Danish residents (13).

Stress cohort

We previously published a detailed description of the original stress cohort (14). In brief, the original stress cohort contained all Danish-born residents of Denmark with a reaction to severe stress disorder diagnosed at a psychiatric treatment facility between January 1, 1995, and December 31, 2011. For the purposes of the current study, we restricted the sample to persons aged 40 years or older ($n = 38,386$). The date of the first recorded diagnosis was defined as a cohort member's index date. All cohort members were characterized according to their incident stress diagnosis.

Data on stress diagnoses at psychiatric treatment facilities were drawn from the national Danish Psychiatric Central Research Registry, which has recorded inpatient and outpatient psychiatric encounters since 1969 and contains up to 20 diagnoses per treatment episode (15, 16). A validation study showed moderate to high validity across stress diagnoses when compared with an independent reassessment of symptoms (17).

Since the original stress cohort was developed, it has been augmented with persons who received their stress diagnosis only at a somatic treatment facility ($n = 8,661$) between January 1, 1995, and December 31, 2011, increasing the total stress cohort to 47,047 persons. Data on stress diagnoses at these hospitals were obtained from the Danish National Patient Registry. The Danish National Patient Registry has covered all inpatient treatment in general hospitals in Denmark since 1977 and outpatient clinic and emergency room visits since 1995 (18).

Comparison cohort

We created a comparison cohort of Danish-born residents of Denmark who had not received a stress disorder diagnosis at the time of their matched stress cohort member's diagnosis, aged 40 years or older ($n = 232,141$). Comparison cohort members were individually matched to stress cohort members in a ratio of 5 to 1 on sex and exact age on the index date. The comparison cohort was sampled from the Danish Civil Registration System, which contains demographic data and registers all changes in residence and vital status (13, 19).

Covariates

Data on sex and marital status were obtained from the Danish Civil Registration System (12). The Danish Psychiatric Central Research Registry and Danish National Patient Registry provided data on psychiatric comorbidity prior to a stress disorder diagnosis, including depression diagnoses, anxiety diagnoses, alcohol abuse and dependence diagnoses, and drug abuse and dependence diagnoses. We used the Danish National Patient Registry to compute a Charlson Comorbidity Index (CCI) score for each person included in the study. The Charlson Comorbidity Index score provides a measure of overall hospital-diagnosed comorbidity burden. The measure was modified in this study to exclude diagnoses of dementia (20).

Outcome data

We obtained data on dementia diagnoses from the Danish Psychiatric Central Research Registry and Danish National Patient Registry. The *International Classification of Diseases, Tenth Revision*, codes for all variables included in the analyses are listed in Web Table 1 (available at https://academic.oup.com/aje).

Analyses

We conducted descriptive and stratified analyses to examine important demographic variables and baseline comorbid disorders across categories of stress diagnoses. We followed all stress cohort and comparison cohort members until the occurrence of a dementia diagnosis, emigration, death, or December 31, 2011, whichever came first. We restricted all analyses to persons without dementia at the start of follow-up, who were aged 40 years or older. Only outcomes occurring 1 year or more after a stress diagnosis were examined, to reduce the potential bias from reverse causation.

We calculated the risk of dementia over the 17-year study period for each stress disorder and comparison cohort as the number of persons who developed dementia divided by the number of persons at risk. We used stratified Cox proportional hazards regression to estimate hazard ratios with 95% confidence intervals for the unadjusted and adjusted associations between each stress disorder type and dementia. Variables were chosen for adjustment based on current knowledge and restricted to those measured before the stress diagnosis. This restriction helped to ensure that they were not on the causal pathway from the stress diagnosis to dementia. Associations were adjusted for the following variables: sex and age (by matching); marital status; diagnoses of depression, anxiety, alcohol abuse/dependence, and drug abuse/dependence; and the Charlson Comorbidity Index score. To examine the interaction between stress disorders and sex in predicting dementia, we calculated the interaction contrast as a measure of the departure from additive effects (21). Results are not presented for

instances in which there were fewer than 5 dementia cases in either the stress disorder cohort or comparison cohort for a given analysis.

A potential major threat to the validity of our results is that underlying cerebrovascular disease might influence the risk of receiving a stress disorder diagnosis and subsequent vulnerability to dementia (22). To address this, we conducted a sensitivity analysis to assess differences in the adjusted hazard ratio across 3 follow-up periods (1–5 years, 6–10 years, and 11–17 years after a stress disorder diagnosis) to examine whether the adjusted hazard ratio attenuates with longer passage of time between incident stress diagnosis and dementia diagnosis. The rationale was that an adjusted hazard ratio that is higher when stress disorder and dementia occur more proximally could indicate a possible shared underlying cause.

Another threat to validity is misclassification of dementia diagnosis. The sensitivity of dementia diagnoses in the Danish registries is 86%; it is unknown whether this differs according to stress disorder status (23). It is possible that persons with stress disorders more frequently encounter the medical system than persons without stress disorders do, and that they are thus more likely to receive a dementia diagnosis or receive it earlier in the clinical course. We conducted a bias analysis to understand the potential impact of these forms of misclassification on our observed associations (24). We assumed for these analyses that specificity of dementia diagnosis was 100% (i.e., all persons without dementia are correctly classified as not having dementia). For the assessment of nondifferential misclassification of dementia by stress disorder, we set sensitivity of dementia diagnosis to 86%. For the assessment of differential misclassification of dementia by stress disorder, we set sensitivity of dementia diagnosis to 90% for the stress disorder cohort and 70% for the comparison cohort.

This work was approved by the Institutional Review Board of Boston University, the Danish Health and Medicines Authority, and the Danish Data Protection Agency (record no. 2012-41-0841).

RESULTS

We identified 4,389 persons with an acute stress reaction, 2,189 persons with PTSD, 27,100 persons with an adjustment disorder, 1,394 persons with other stress reactions, and 11,975 persons with unspecified stress reactions without prevalent dementia. Persons with stress disorders had a median of 6.1 years follow-up, while persons in the comparison cohort had a median of 6.8 years follow-up. Median age at time of cohort entry was 51 years. During the study period, 1,364 persons in the stress cohort were diagnosed with dementia. Table 1 presents additional descriptive characteristics of the stress and comparison cohorts.

Risk of dementia

The risk of dementia during the 17 years of follow-up ranged from 3.9% for persons with acute stress reaction to 6.2% for persons with adjustment disorder and unspecified stress disorders (Table 2). The risk of dementia over the 17-year study period was consistently higher in the stress cohort than in the comparison cohort.

Associations between stress disorders and dementia

An association with dementia was found for each stress disorder diagnosis after adjustment for sex, baseline age, marital status, depression diagnoses, substance abuse/dependence diagnoses and Charlson Comorbidity Index score. Persons with acute stress reaction had 1.6 times the rate of dementia compared with comparison cohort members (95% CI: 1.2, 2.1). Persons diagnosed with PTSD had 2.0 times the rate of dementia compared with members of the comparison cohort (95% CI: 1.3, 3.2), while persons diagnosed with adjustment disorder had 2.4 times the rate of dementia compared with members of the comparison cohort (95% CI: 2.2, 2.7). The adjusted associations between the unspecified stress disorders and dementia were 2.8 (95% CI: 1.5, 5.1) and 2.2 (95% CI: 1.8, 2.6) for other stress reactions and unspecified stress disorders, respectively (data not shown).

Table 3 displays the sex-stratified dementia rates and the interaction contrasts describing the interaction between stress disorders and sex in relation to dementia. There is evidence of interaction between sex and each stress disorder, with the exception of PTSD, such that men with stress disorders experience a higher rate of dementia than would be expected based on the individual associations of sex and stress disorders on dementia. Interestingly, for PTSD, the interaction contrasts indicate that it is women with stress disorders who experience a higher rate of dementia than is expected (104 extra cases per 100,000 person-years).

Sensitivity analyses

In the sensitivity analysis to assess differences in adjusted hazard ratios across 3 time periods within the overall study period, we found no consistent pattern of changes in magnitude over time across types of stress disorders or across time intervals. In some instances, the effect was strongest when a stress disorder and dementia diagnosis occurred within 1–5 years of each other. In many other cases the strongest effect was found for the middle or last period or was consistent across time periods (Web Table 2).

We conducted a second sensitivity analysis to examine the impact of nondifferential and differential misclassification of dementia diagnosis. Web Table 3 displays the uncorrected and bias-adjusted estimates under the different bias scenarios. Assuming a valid bias model, these results indicate that nondifferential misclassification of dementia diagnosis by stress disorder would have negligible impact on our observed associations. Results further show that differential misclassification of dementia diagnosis by stress disorder would have caused some inflation away from the null in our observed estimates but still would not account for our entire observed associations between stress disorders and dementia.

DISCUSSION

We examined the risk of dementia among persons with a range of stress disorders in a single population-based sample with nearly complete follow-up. Risk of dementia during the study period was higher for persons with stress disorders than for persons without these diagnoses, and this finding was consistent across stress diagnoses. Further, persons with stress disorders had a higher rate of dementia when compared with a cohort

Table 1. Baseline Characteristics (%) in Stress Disorder Cohorts and Associated Comparison Cohorts, Denmark, 1995–2011

Characteristic	Acute Stress Reaction Comparison		PTSD Comparison		Adjustment Disorder Comparison		Other Stress Reactions Comparison		Unspecified Stress Disorder Comparison	
	Acute Stress Reaction Cohort (n = 4,389)	Comparison Cohort (n = 21,679)	PTSD Cohort (n = 2,189)	Comparison Cohort (n = 10,853)	Adjustment Disorder Cohort (n = 27,100)	Comparison Cohort (n = 133,621)	Other Stress Reactions Cohort (n = 1,394)	Comparison Cohort (n = 6,911)	Unspecified Stress Disorder Cohort (n = 11,975)	Comparison Cohort (n = 59,077)
Sex										
Female	57	57	59	59	61	61	71	71	63	63
Male	43	43	41	41	39	39	29	29	37	37
Age group, years										
40–59	80	80	87	87	76	76	85	85	75	75
≥60	20	20	13	13	24	24	15	15	25	25
Marital status										
Married/ partnered	48	65	64	66	45	65	57	65	61	65
Divorced	25	13	23	13	26	13	22	15	23	13
Widowed	9	5.5	7.2	4.5	11	7.4	5.2	5.1	9.3	6.8
Never married	14	13	13	13	13	11	13	13	14	13
Unknown	3.8	3.0	3.1	3.4	4.0	3.3	2.6	2.6	3.4	2.7
Depression diagnoses	12	0.5	9.9	0.5	16	0.5	9.4	0.4	11	0.6
Alcohol abuse/ dependence diagnoses	11	1.3	6.8	1.3	13	1.1	6.8	1.3	10	1.3
Drug abuse/ dependence diagnoses	3.7	0.3	2.9	0.3	3.9	0.3	1.1	0.3	3.2	0.4
Anxiety diagnoses	3.8	0.2	4.6	0.3	5.3	0.2	3.1	0.3	4.0	0.3
CCI score >1	22	13	20	11	24	13	20	12	28	15

Abbreviations: CCI, Charlson Comorbidity Index; PTSD, posttraumatic stress disorder.

Table 2. Risk of Dementia Among Persons With Subtypes of Stress Disorders and Their Associated Comparison Cohorts, Denmark, 1995–2011

Subtype Group and Comparison Cohort	Median Follow-up, years	Dementia Risk[a]	
		%	95% CI
Acute stress reaction	5.6	3.9	3.0, 4.9
Comparison cohort	6.2	2.9	2.5, 3.4
PTSD	6.6	4.8	3.1, 7.0
Comparison cohort	6.8	2.4	1.8, 3.1
Adjustment disorder	7.1	6.2	5.7, 6.7
Comparison cohort	8.0	3.5	3.3, 3.7
Other reactions to severe stress	5.4	5.8	3.4, 8.9
Comparison cohort	5.6	3.0	1.9, 4.6
Unspecified stress disorders	4.7	6.2	4.6, 8.1
Comparison cohort	5.0	3.6	3.1, 4.1

Abbreviations: CI, confidence interval; PTSD, posttraumatic stress disorder.

[a] Risk was calculated as the number of persons who developed dementia divided by the number of persons at risk.

not diagnosed with stress disorder. This was true across all 5 stress disorder diagnoses. This study extends previous work in this area by examining stress disorders that have both a potentially severe and chronic course (e.g., PTSD) and stress disorders that likely represent subsyndromal "catch-all" groups of persons who are experiencing distress following a stressful or traumatic event but do not meet diagnostic criteria for one of the other disorders (e.g., unspecified stress disorders).

Another way in which the current study extends existing evidence is by examining the interaction between sex and stress disorders in association with dementia. For almost all stress disorders, we observed an excess number of dementia cases among men compared with what would have been expected based on the observed association in women. Conversely, an excess number of cases of dementia was found among women with PTSD. In the United States, a study using longitudinal data from the Kaiser Permanente Northern California health system reported similar relative associations between PTSD and dementia for men and women (6). The calculation of the interaction contrast, as the departure from additive effects, accounts for potential differences in the background rates of dementia in men and women (which would affect the calculation of stratum-specific relative estimates) and provided evidence of a higher rate of dementia among women with PTSD.

Many potential mechanisms for the association between stress disorders and dementia have been hypothesized. These include hippocampal atrophy resulting from stress, which increases risk for cognitive deficits; alterations in the hypothalamic-pituitary-adrenal axis and proinflammatory cytokines; and changes in health-related behaviors such as exercise, management of chronic diseases, and smoking (10, 25). It also has been hypothesized that stress, specifically combat-related PTSD, and dementia might share a causal antecedent (e.g., intelligence (26)) that explains the observed association. We thus conducted a bias analysis to examine whether a causal antecedent of both stress disorder and dementia might partly explain our results. We ascertained whether associations were strongest when stress disorder and dementia diagnoses occurred close together in time. The pattern of results indicated that it is unlikely that a common underlying cause of both stress disorders and dementia could fully account for the observed associations. It will be important for future research to address both precipitating factors that might potentiate risk for both diagnostic responses to stress and dementia and also mechanisms through which persons with stress disorders might be at increased risk of dementia.

Strengths of this study include use of clinician-derived data from a nationwide cohort with a substantial follow-up period and limited loss to follow-up. In addition, use of prospective data gleaned from clinical diagnoses ensures that recall bias did not influence our results. In addition to limitations described above, others are important to note. It is possible that detection bias explains some of our results (i.e., dementia might have been more frequently diagnosed among persons with stress disorders who were receiving treatment). Our bias analysis demonstrates that while this type of bias might have caused a slight inflation away from the null, it does not fully account for our observed associations (assuming a valid bias model). We used a specificity of 100% in these bias analyses. Using a specificity less than 0.99 in our bias analyses generated

Table 3. Rates and Interaction Contrasts for Sex Differences in the Association Between Stress Disorders and Dementia, Denmark, 1995–2011

Stress Disorder	Dementia Rate According to Sex/100,000 Person-Years				IC Per 100,000 Person-Years	95% CI
	Men		Women[a]			
	Stress Cohort	Comparison Cohort	Stress Cohort	Comparison Cohort		
Acute stress reaction	415.0	174.6	275.2	194.4	159.6	5.0, 314.3
PTSD	204.9	107.4	345.7	144.1	−104.1	−285.0, 76.8
Adjustment disorder	478.2	171.0	532.1	251.4	26.4	−43.2, 96.1
Other stress reactions	505.7	171.7	335.2	130.7	129.4	−218.6, 477.4
Unspecified stress disorder	476.8	166.9	434.9	210.0	85.0	−32.4, 202.4

Abbreviations: CI, confidence interval; IC, interaction contrast; PTSD, posttraumatic stress disorder.

[a] Women were used as the reference group for the interaction-contrast calculation.

negative cell counts in the bias-adjusted data. Specificity of 99% implies a false-positive risk of 1%, which would mean that between one-half and one-third of our observed dementia cases in the comparison cohorts (where risks were about 2% or 3%) would have been false cases. This proportion of false diagnoses seems implausible, which explains why using specificity of less than 99% resulted in implausible bias adjustments. The specificity of dementia in a Medicare claims data set has been found to be 0.89 (27), a specificity that would imply 11% false-positive disease risk, which exceeds the observed risk in all of our exposure categories. This value for the specificity is clearly incompatible with our results.

Another concern was that we were unable to examine all associations of interest due to sample size constraints. Medication data and data on education were not available in the data source used for the current project, and thus we were unable to examine the potential impact of these variables on observed associations between stress disorders and dementia. It is unclear how adjustment for these variables would have altered our observed associations. Finally, it is possible that there are additional confounders of the association between stress disorders and dementia for which we were unable to adjust. The impact of potential unmeasured confounding on the observed results in also unknown.

Taken together, our study results support previous evidence indicating an increased risk of dementia among persons with stress disorders. The study also contributed novel information regarding associations across a range of stress responses and interactions with sex.

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