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ORIGINAL ARTICLE



# Adjustment disorder and type-specific cancer incidence: a Danish cohort study

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**ABSTRACT**

**Background:** Although adjustment disorder is common, there is a dearth of research on its physical health consequences. Earlier studies, biological mechanisms and stress-related behaviors suggest that cancer may be a potential sequelae of adjustment disorder. This study examined the association between adjustment disorder and type-specific cancer incidence in a nationwide cohort.

**Methods:** Data were obtained from the comprehensive nationwide medical and administrative registries of Denmark. We calculated the incidence of type-specific cancers from 1995 to 2013 in patients with a prior adjustment disorder diagnosis ($n = 58{,}712$), and compared it with the incidence in the general population by calculating standardized incidence ratios (SIRs) with accompanying 95% confidence intervals (CIs). SIRs were adjusted using semi-Bayes shrinkage.

**Results:** The SIR for any type of cancer was 1.0 (95% CI: 0.99, 1.1). Adjustment disorder was associated with a 10% lower rate of immune-related cancers (SIR = 0.9, 95% CI: 0.84, 0.97) and with a 20% higher rate of smoking- and alcohol-related cancers (SIR = 1.2, 95% CI: 1.1, 1.3). We found null associations for hematological (SIR = 1.1, 95% CI: 0.89, 1.3) and hormone-related (SIR = 0.98, 95% CI: 0.91, 1.1) malignancies. After semi-Bayes adjustment, type-specific cancer SIRs indicated no association between adjustment disorder and cancer incidence.

**Conclusions:** This study provides persuasive evidence for a null association between adjustment disorder and type-specific cancer incidence in a nationwide study cohort.

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## Introduction

Adjustment disorder is a psychiatric diagnosis characterized by extreme emotions or behavioral symptoms in response to a stressor, with impairment of social or occupational functioning [1]. It is classified by International Classification of Disease, 10th revision (ICD-10) among stress-related disorders including acute stress reactions, posttraumatic stress disorder and other reactions to severe stress. The key distinction between adjustment disorder and other stress-related disorders is that it is diagnosed following a significant life stressor that is not necessarily traumatic (e.g., divorce, death of a loved one) but from which one is having difficulty recovering. The prevalence of adjustment disorder varies across patient populations [2]. Previous studies have found that the prevalence of adjustment disorder was 16–19% among patients after trauma exposure [3], 25–32% among patients who were undergoing or had completed cancer treatment [4], and 3% among primary care patients [5]. Our earlier nationwide Danish cohort study found that two-thirds of incident ICD-10 severe stress and adjustment disorder diagnoses between 1995 and 2011 were for adjustment disorder [6]. Although adjustment disorder is common, there has been little research to date on its sequelae [2,7]. Thus, little is known about how adjustment disorder influences physical health. In contrast, there have been decades of research into the role of stress in general in the etiology of somatic illnesses, including cancer [8–10]. Potential biological mechanisms underlying the association between stress and cancer include dysregulation of the hypothalamic pituitary adrenal (HPA) axis, increased inflammation, inhibited repair of damaged DNA and increased oncogenic mutations [11–14]. Genetic mutations, neuroendocrine function and cytotoxic immunological functions have also been implicated in the pathways from stress to the development of cancer [15,16]. Hypothesized behavioral mechanisms include stress-induced adverse behaviors such as smoking, excessive alcohol consumption, poor diet, lack of exercise, obesity, poor sleep and lower treatment adherence [15].

In a study of women in the Finnish Twin Cohort, stressful life events such as the death of a husband were associated with an increased risk of breast cancer when compared to not having any major stressful life events [9]. A cohort study in Israel found that bereaved parents had increased incidence

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of lymphatic and hematopoietic malignancies compared with non-bereaved parents [17]. A prospective study in Scotland found evidence for elevated incidence of prostate and breast cancers in males and females who reported moderate and high stress levels, compared with those who reported low stress levels [18]. In a Swedish cohort, women who reported experiencing stress had a higher rate of breast cancer compared with women reporting no stress [19]. In a follow-up study using national registry data in Denmark, the death of a child was associated with an increased risk for smoking-related malignancies, but no association was found with breast carcinoma, alcohol-related malignancies, viral/immune-related malignancies or hormone-related malignancies [20]. In contrast, several studies have found inverse associations between perceived stress and cancer. Prospective studies of Danish women found that women with high levels of perceived stress had decreased risk of breast cancer, colorectal cancer and endometrial cancer compared to women with low levels of stress [21–23].

Although some studies have found associations between stress and cancer, most have found no evidence of an association. A meta-analysis showed that 77% of 165 studies reported null associations between psychosocial stress and cancer incidence [15]. However, subgroup meta-analyses by cancer type revealed that stress-related psychosocial factors were associated with higher lung cancer incidence [15].

Research to date has yielded inconsistent findings and this may be due to methodological differences across studies. Studies differ in the types of stress measured, types of cancer examined and length of follow-up time. There is a need for well-designed cohort studies to elucidate potentially important associations between stress and cancer [24,25]. The current study fills this gap by examining the incidence of various cancer types in a nationwide cohort of patients with a prior diagnosis of adjustment disorder between 1995 and 2013.

## Methods

### Source population and data collection

All study data were derived from Danish population-based civil and medical registries. These registries can be linked together unambiguously at the individual level by using the Central Personal Registry (CPR) number—a unique identifier assigned to all residents of Denmark [26]. Our source population consisted of Danish residents aged $\geq$15 years between 1 January 1995 and 30 January 2013. We used the Danish Psychiatric Central Research Register (DPCRR) and the Danish National Patient Registry (DNPR) to identify an index cohort comprised of all persons in the source population with at least one incident ICD-10 diagnosis of adjustment disorder [6]. The DPCRR has collected inpatient data since 1969 and outpatient data since 1995, recording treatment dates and up to 20 diagnoses for each registered treatment session [27,28]. The DNPR has recorded diagnoses made during inpatient stays at non-psychiatric hospitals since 1977 and during outpatient visits and emergency department encounters since 1995 [29]. In addition to identifying patients diagnosed with adjustment disorder, we used the DNRP to ascertain medical comorbidities, which we summarized for each subject by calculating a Charlson Comorbidity Index (CCI) score [30,31].

We compared type-specific cancer incidence rates among members of the adjustment disorder cohort with corresponding rates in the general population. Date of birth, gender and vital status were ascertained from the Danish Civil Registration System. Incident malignancies were identified by linking to the Danish Cancer Registry (DCR), which has recorded cancer diagnoses since 1943. Diagnoses in the DCR have been re-coded to conform with ICD-10 classifications [32]. Supplementary Appendix 1 lists all diagnoses assessed for the cohort, with corresponding ICD-10 codes.

### Definitions of analytic variables

We restricted the cohort to subjects who were alive and without a cancer history one year after an adjustment disorder diagnosis. This ensured that the cancer diagnosis itself did not contribute to the adjustment disorder. Incident malignancies were grouped into the following categories: (1) all cancers, (2) hematologic malignancies, (3) immune-related cancers, (4) smoking and alcohol-related cancers, (5) hormone-related cancers and (6) all other cancer types. Age and calendar period were defined at the beginning of follow-up and were categorized into 5-year intervals for standardization.

### Statistical analysis

To calculate the expected number of type-specific incident cancer cases during the follow-up period, we first summed person-years of follow-up for the adjustment disorder cohort within joint strata of sex, 5-year age group and 5-year calendar period. We multiplied these sums by the stratum-specific cancer incidence rates in the source population, yielding the number of type-specific cancer diagnoses expected among the adjustment disorder cohort, had its members experienced the same cancer rate as the source population. We then divided the observed number of type-specific cancer cases in the adjustment disorder cohort by the expected number of cases to obtain the standardized incidence ratio (SIR) associating adjustment disorder with cancer incidence. We calculated accompanying 95% confidence intervals assuming a Poisson distribution, using exact calculations when there were fewer than 10 observed cases, and relying on the Byar approximation otherwise [33]. We limited our analysis to cancer types with at least 5 observed cases in the adjustment disorder cohort.

### Semi-Bayes adjustment

To account for multiple estimation, we subjected the type-specific cancer SIRs to semi-Bayes shrinkage [34]. This technique attenuates individual associations toward the overall mean in proportion to their variance, thus de-emphasizing imprecisely measured, high-magnitude associations. This

adjustment helps to avoid unproductive investigation of findings that are likely to be spurious. For semi-Bayes adjustment, we specified a true population variance of 0.281, which is consistent with 95% of SIRs falling between 0.5 and 4. We also ranked the type-specific log-SIRs by magnitude and plotted them against the inverse normal of rank percentile (INRP). We overlaid on this plot (1) the semi-Bayes log-SIRs and (2) a line of predicted log-SIRs from the inverse variance-weighted regression of observed log-SIRs on INRP. In addition to providing a visual comparison of pre- and post-shrinkage estimates, this plot evaluates whether the set of cancer-specific associations are consistent with individual associations drawn from a null-centered Gaussian distribution [35].

Analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC).

## Results

One year after diagnosis of an adjustment disorder, 58,712 patients were alive and without a cancer history (Table 1). Median follow-up time for a first incident cancer was 7.2 years (interquartile range: 3.6 to 12.1 years). Fifty-nine percent of the cohort was female and only 17% of subjects had one or more comorbidities. The prevalence of chronic alcoholism diagnostic codes was relatively low (5.4%), but more than 25% of the cohort had diagnosed substance abuse (Table 1).

Table 2 presents the SIRs associating diagnosis of an adjustment disorder with broad groupings of cancer. For any cancer, we observed a precisely-measured null association (SIR = 1.0, 95% CI: 0.99, 1.1). We also observed a null association for hematological malignancies (SIR = 1.1, 95% CI: 0.89, 1.3) and for hormone-related malignancies (SIR = 0.98, 95% CI: 0.91, 1.1). Adjustment disorder was associated with a 10% lower rate of immune-related cancer incidence (SIR = 0.90, 95% CI: 0.84, 0.97) and with a 20% higher rate of smoking- and alcohol-related cancer incidence (SIR = 1.2, 95% CI: 1.1, 1.3). Figure 1 depicts these associations within strata of sex, presence of diagnosed substance abuse, and presence of diagnosed chronic alcoholism. Associations with smoking- and alcohol-related cancers were near null in the strata representing absence of diagnosed substance abuse or chronic alcoholism.

Table 3 shows the original SIRs and the semi-Bayes shrinkage estimates for 33 type-specific cancers. The cancer types are arranged in rows representing increasing magnitude of the original SIRs. Semi-Bayes shrinkage had the expected effect of attenuating estimates that were high magnitude and measured with poor precision. For example, the original SIR for gallbladder cancer, which affected only 6 subjects in the adjustment disorder cohort, was strongly protective but imprecisely measured (SIR = 0.63, 95% CI: 0.23, 1.4); its corresponding semi-Bayes estimate was closer to the null ($SIR_{SB}$ = 0.81, 95% CI: 0.41, 1.6). In comparison, prostate cancer—which affected 125 subjects in the adjustment disorder cohort—showed a near-null association measured with good precision (SIR = 0.88, 95% CI: 0.73, 1.1). In this case, the semi-Bayes estimate was nearly identical to the original estimate ($SIR_{SB}$ = 0.89, 95% CI: 0.72, 1.1). In Figure 2, the original and attenuated SIRs are overlaid and plotted according to the inverse normal of the rank percentile of the original SIR. The left-to-right ordering in the plot corresponds to the top-to-bottom ordering in Table 3; however, it is important to note that some cancer types had the same association with adjustment disorder and are therefore superimposed on one another in Figure 2. Examination of Figure 2 shows that the line of modeled SIRs very nearly crosses through the origin (where log-SIR and INRP both equal zero), and that the original log-SIRs closely adhere to the line of predicted associations. Together, these features indicate that type-specific cancer associations are consistent with random draws from an underlying null-centered Gaussian distribution.

**Table 1.** Characteristics of patients diagnosed with adjustment disorder who were alive and without a cancer history one year after diagnosis ($n$ = 58,712).

| Characteristic | |
|---|---|
| Sex, *n* (%) | |
| Male | 23,806 (41) |
| Female | 34,906 (59) |
| Age at diagnosis of adjustment disorder, *n* (%) | |
| 16–39 years | 34,757 (59) |
| 40–59 years | 18,473 (31) |
| ≥60 years | 5482 (9.3) |
| Charlson Comorbidity Index, *n* (%) | |
| 0 | 48,850 (83) |
| 1 | 8761 (15) |
| 2 | 902 (1.5) |
| 3 | 199 (0.3) |
| Substance abuse, *n* (%) | |
| Chronic alcoholism | 3155 (5.4) |
| Other substance abuse | 15,578 (27) |
| Person-years at risk, median (q1, q3) | 7.2 (3.6, 12.1) |

Denmark, 1995–2013.

**Table 2.** Associations between adjustment disorder and cancer types, Denmark, 1995–2013.

| Cancer type | Observed events | Expected events[a] | SIR (95% CI) |
|---|---|---|---|
| Any cancer | 2558 | 2472 | 1.0 (0.99, 1.1) |
| Hematological | 137 | 129 | 1.1 (0.89, 1.3) |
| Hormone-related | 624 | 636 | 0.98 (0.91, 1.1) |
| Immune-related | 784 | 869 | 0.90 (0.84, 0.97) |
| Smoking and alcohol-related | 799 | 651 | 1.2 (1.1, 1.3) |

[a]Rounded to the nearest whole number.

## Discussion

We measured the impact of an adjustment disorder diagnosis on the incidence of 33 type-specific malignancies in a Danish nationwide cohort study. We found a null association with cancer incidence overall, but when this was parsed into broad cancer types, a protective association with immune-related cancers and a causal association with smoking- and alcohol-related cancers emerged. The protective association with immune-related cancers appeared to be driven by skin cancers, which showed modestly protective type-specific associations that became near-null upon semi-Bayes adjustment. The causal association with smoking- and alcohol-related cancers was attenuated within strata of no substance abuse and no chronic alcoholism, suggesting that the overall

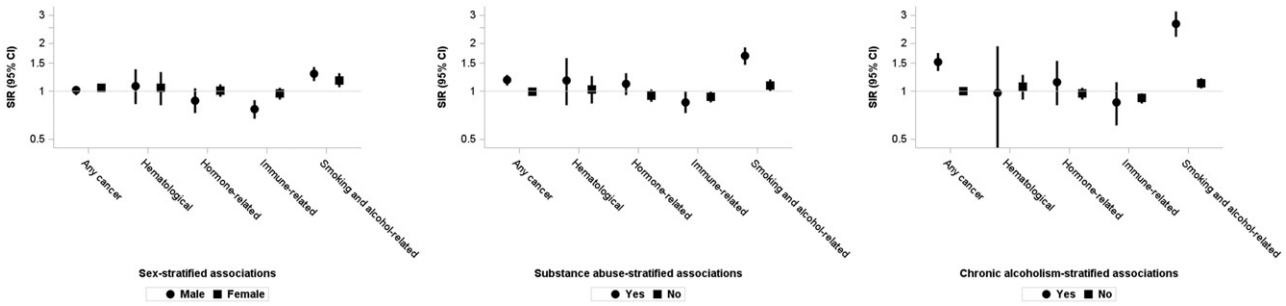


**Figure 1.** Associations between adjustment disorder and cancer types, stratified by sex, presence of substance abuse, and presence of chronic alcoholism, Denmark, 1995–2013.

**Table 3.** Standardized incidence ratios, before and after semi-Bayes shrinkage, associating adjustment disorder with type-specific cancer incidence.

| Cancer type | Observed events | Expected events[a] | Original SIR (95% CI) | Semi-Bayes SIR (95% CI) |
|---|---|---|---|---|
| Gallbladder | 6 | 10 | 0.63 (0.23, 1.4) | 0.81 (0.41, 1.6) |
| Skin, melanoma | 94 | 131 | 0.72 (0.58, 0.88) | 0.73 (0.58, 0.93) |
| Stomach | 22 | 27 | 0.81 (0.51, 1.2) | 0.85 (0.56, 1.3) |
| Ovary/fallopian tube | 37 | 45 | 0.83 (0.58, 1.1) | 0.86 (0.61, 1.2) |
| Multiple myeloma | 15 | 18 | 0.85 (0.48, 1.4) | 0.90 (0.55, 1.5) |
| Endocrine gland | 17 | 20 | 0.86 (0.50, 1.4) | 0.91 (0.57, 1.5) |
| Rectum | 63 | 73 | 0.86 (0.66, 1.1) | 0.87 (0.66, 1.2) |
| Prostate | 125 | 142 | 0.88 (0.73, 1.1) | 0.89 (0.72, 1.1) |
| Uterus | 48 | 54 | 0.88 (0.65, 1.2) | 0.90 (0.66, 1.2) |
| Skin, non-melanoma | 589 | 664 | 0.89 (0.82, 0.96) | 0.89 (0.77, 1.0) |
| Bladder | 33 | 37 | 0.90 (0.62, 1.3) | 0.92 (0.65, 1.3) |
| Leukemia | 38 | 42 | 0.90 (0.64, 1.2) | 0.92 (0.66, 1.3) |
| Small intestine | 5 | 5 | 0.93 (0.30, 2.2) | 1.0 (0.50, 2.1) |
| Colon | 128 | 135 | 0.95 (0.79, 1.1) | 0.95 (0.77, 1.2) |
| Breast | 414 | 397 | 1.04 (0.95, 1.2) | 1.0 (0.89, 1.2) |
| Testes | 33 | 29 | 1.2 (0.79, 1.6) | 1.2 (0.80, 1.7) |
| Non-Hodgkin's lymphoma | 68 | 58 | 1.2 (0.91, 1.5) | 1.2 (0.90, 1.5) |
| Peritoneum/connective tissue | 18 | 15 | 1.2 (0.69, 1.9) | 1.2 (0.73, 1.9) |
| Tongue | 10 | 9 | 1.2 (0.56, 2.1) | 1.2 (0.65, 2.1) |
| Esophagus | 26 | 22 | 1.2 (0.78, 1.7) | 1.2 (0.80, 1.8) |
| Brain | 37 | 31 | 1.2 (0.85, 1.7) | 1.2 (0.85, 1.7) |
| Kidney | 44 | 35 | 1.3 (0.91, 1.7) | 1.2 (0.91, 1.7) |
| Nasal cavity/middle ear | 5 | 3 | 1.3 (0.41, 3.0) | 1.2 (0.58, 2.5) |
| Cervix | 58 | 45 | 1.3 (0.97, 1.7) | 1.3 (0.96, 1.7) |
| Lung | 297 | 210 | 1.4 (1.3, 1.6) | 1.4 (1.2, 1.7) |
| Liver | 22 | 15 | 1.4 (0.90, 2.2) | 1.4 (0.91, 2.1) |
| Hodgkin's lymphoma | 16 | 11 | 1.5 (0.83, 2.4) | 1.4 (0.85, 2.2) |
| Pancreas | 66 | 46 | 1.5 (1.1, 1.8) | 1.4 (1.1, 1.9) |
| Lymph node | 50 | 34 | 1.5 (1.1, 2.0) | 1.5 (1.1, 2.0) |
| Tonsil/pharynx | 39 | 23 | 1.7 (1.2, 2.4) | 1.7 (1.2, 2.6) |
| Larynx | 27 | 14 | 1.9 (1.2, 2.7) | 1.8 (1.2, 2.6) |
| Anus | 16 | 8 | 2.1 (1.2, 3.5) | 1.9 (1.2, 3.0) |
| Mouth | 37 | 13 | 2.8 (2.0, 3.8) | 2.6 (1.8, 3.6) |

Limited to malignancies with at least 5 observed events in the adjustment disorder cohort. Denmark, 1995–2013.
[a]Rounded to the nearest whole number.

association is confounded by substance abuse and correlated behaviors (e.g., smoking), for which we could not adjust directly.

When we evaluated specific cancer types, associations ranged from strongly protective (e.g., for gallbladder cancer, SIR = 0.63, 95% CI: 0.23, 1.4) to strongly causal (e.g., for mouth cancers, SIR = 2.8, 95% CI: 2.0, 3.8), although most associations were null or near null. Semi-Bayes adjustment of the type-specific cancer SIRs attenuated most of the strongly protective and strongly causal associations, and the overall distribution of the original type-specific SIRs was consistent with associations drawn at random from an underlying, null-centered, normal distribution. We interpret our evidence *in toto* as indicating no direct association between adjustment disorder and cancer incidence.

Key strengths of our study are enrollment of a large cohort of persons diagnosed with adjustment disorder ($n = 58{,}712$) using Denmark's nationwide medical and psychiatric registries. The large size of the cohort allowed us to explore type-specific cancer diagnoses (including rare malignancies), in addition to traditional groupings of related malignancies. Potential selection bias was minimized through use of nationwide registries to identify subjects with minimal exclusion criteria and little loss to follow-up. Classification of adjustment disorder in the DPCRR (the Registry from which we identified the majority of the adjustment disorder cohort)

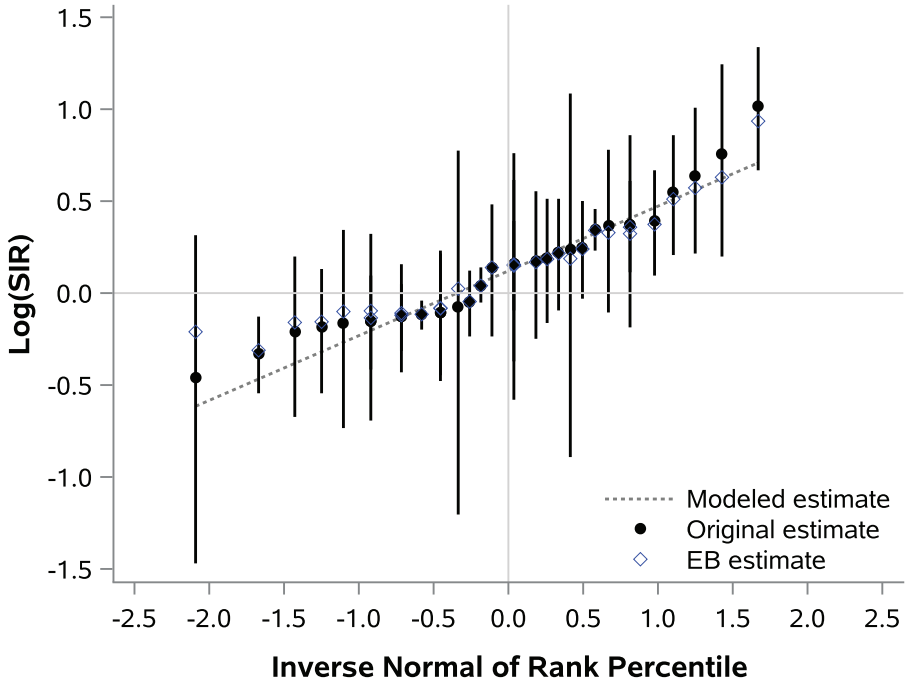


**Figure 2.** Associations between adjustment disorder and type-specific cancer incidence, plotted according to the inverse normal of rank percentile. Solid circles indicate original log SIR estimates, with accompanying 95% confidence intervals shown as error bars. The dashed line represents predicted log SIRs calculated from the inverse variance-weighted regression of the observed log SIR on the inverse normal of rank percentile. Open diamonds indicate corresponding semi-Bayes point estimates. Associations are ordered left-to-right according to the list of observed SIRs in Table 3. Note that some cancer types with equal SIR values are overlapping in the plot.

was excellent when validated against medical records, with a positive predictive value of 94% [27,36]. Another study strength was ascertainment of cancer outcomes from the DCR, which has logged newly diagnosed malignancies across Denmark since 1943, and in which 95%—98% of records have been found to be valid [32,37].

Our study is limited by the potential for misclassification of adjustment disorder, residual confounding by unmeasured factors, and by modest follow-up time. While the classification of adjustment disorder in the index cohort is likely highly specific, we do not expect that the reference cohort was free of adjustment disorder or history of other stress disorders, as these conditions may go undiagnosed. The base population cancer incidence rates that we used to calculate SIRs therefore may be influenced by undiagnosed adjustment disorder/severe stress, which would bias our results toward the null. We also were unable to adjust for potential confounding by smoking and alcohol use, which are expected to be positively associated with adjustment disorder. Uncontrolled confounding by these factors could readily explain the higher incidence of smoking- and alcohol-related cancers we observed. At the same time, stress disorders can give rise to unhealthy behaviors such as smoking and drinking, suggesting that such behaviors mediate (and do not confound) associations. We also acknowledge that each type-specific cancer has its own set of candidate confounders that we could not account for (e.g., reproductive history for breast cancer). Finally, our median follow-up period after adjustment disorder diagnosis was 7.2 years. As stress pathways may have a longer induction period for cancer development, our follow-up period could have been too short to detect associations. Future research on this topic should therefore focus on study populations with longer available follow-up.

Our study is consistent with other epidemiologic studies on the topic of stress and cancer incidence. We found no association between adjustment disorder and overall cancer incidence but there was evidence of a causal association with smoking-related cancers. These findings align with the results from a meta-analysis which found that stressful life experiences were not related to increased cancer incidence, but that stress-related psychosocial factors were associated with higher incidence of lung cancer [15]. A recent study of posttraumatic stress disorder using a similar Danish population-based study design also found no evidence for associations with type-specific cancer incidence [25]. Other studies using a variety of source populations—some with superior ability to control for behavioral confounders such as smoking and alcohol—also showed null associations [38–41]. Our results are largely inconsistent with studies which have identified associations between stress and cancer. Previous studies have been limited by use of self-reports of stress whereas the current study utilized ICD-10 diagnoses of adjustment disorder which enhances the validity of our results.

In summary, we found no evidence for associations between diagnosed adjustment disorder and incidence of 33 type-specific cancers in a nationwide Danish cohort. Replication of these results in study populations with longer follow-up and detailed data on potentially confounding (or mediating) lifestyle and behavioral factors is warranted.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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