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An analysis of the relative and absolute incidence of somatic morbidity in patients with affective disorders—A nationwide cohort study

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ABSTRACT

Background: Patients with affective disorder seem to experience higher risks of several somatic diseases, but no studies have provided estimates of both absolute and relative risks for these diseases in the same population. Methods: A prospective cohort of all patients age ≥18 years old with a hospital contact with affective disorder between 1997-2014 (n=246,282) and a random sample from the background population (n=167,562) was followed for hospitalizations with cardiovascular disease, diabetes, cancers, chronic obstructive pulmonary disease (COPD), asthma, inflammatory bowel disease, hip fracture, psoriasis, migraine, or dementia. Adjusted absolute and relative risk estimates were calculated using multivariable adjusted Aalen’s additive and Cox proportional hazard regression models.

Results: After adjustments, the absolute risk difference was 130.6 (95% confidence interval [CI] 125.5-135.7) additional cases per 10,000 person-years among affective disorder patients compared to the reference population. The corresponding hazard ratio for any somatic disease was 1.50 (95% CI 1.48-1.52). The strongest associations were found for dementia, hip fracture, COPD, and stroke on both the relative and absolute scale. The patients did not have higher risk of cancers except for lung cancer and brain tumors. Risk estimates tended to be slightly higher for individuals with depression or other affective disorder compared to bipolar disorder.

Limitations: Limitations include use of register-based data, risk of reverse causation and Berkson’s bias.

Conclusions: Patients with affective disorder have both higher absolute and relative risk of most somatic diseases except for cancers. Further identification of the shared mechanisms will facilitate the development of targeted interventions.

1. Introduction

Affective disorders are leading causes of disability and worldwide more than 300 million people per year are diagnosed with an affective disorder (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; World Health Organization, 2008). In addition to suffering during an affective episode, affective disorders are also associated with impaired somatic health (Momen et al., 2020; Penninx et al., 2013), which may partly explain the lower life expectancy of these patients (Nordentoft et al., 2013). Many previous studies have shown a higher risk of developing cardiovascular disease or diabetes among patients with affective disorder. Also, higher risks of other diseases such as cancer, chronic obstructive pulmonary disease (COPD), asthma, autoimmune diseases, and dementia following affective disorders have been reported, albeit with inconclusive findings, especially for cancer (Ahn et al., 2016; Kahan et al., 2018).

Most of these studies have estimated the relative risk of developing somatic diseases among patients with affective disorders. However, when the background risk of a disease is low, the relative risk may obscure the interpretation of the clinical relevance and readers may overestimate the clinical relevance of the relative effects. Contrarily, absolute risk will express the actual number of somatic diseases attributable to being exposed to affective disorder (Xie et al., 2013), which is more relevant from a clinical and public health perspective. Despite this, absolute measures are less often reported, presumably because a statistical method for the estimation of adjusted absolute risks is not part of...
standard statistical software. Further, previous studies have focused on one specific somatic disease and only a few have explored how a range of somatic diseases develop in the same group of patients after being diagnosed with affective disorder.

The aim of this study was to estimate the incidence of somatic morbidity after being diagnosed with affective disorder, using both relative and absolute risk estimates. Together, absolute and relative risk estimates provide a thorough description of the affective disorder patient’s somatic health.

2. Methods

2.1. Study population

In this prospective cohort study, all individuals in Denmark registered with a first-time hospital contact with an affective disorder in the Psychiatric Central Registry (PCR)(Mors et al., 2011) or the National Patient Registry (NPR)(Lynge et al., 2011) between January 1st, 1997 to December 31st, 2014 were included (n=270,428). The PCR and NPR contain information on patients treated at psychiatric departments in Denmark since 1969 and 1977, respectively, include information on date of hospitalization (including outpatient clinics and emergency rooms after 1995) and diagnoses are classified according to the International Classification of Diseases 10th edition (ICD-10). The final study populations included 246,282 individuals with affective disorders and a randomly selected reference population of 167,562 individuals aged ≥18 years. Please see Supplementary Figure 1 for further details. Based on the frequency of the morbidity outcomes studied, the least detectable absolute or relative risk (HR) (β=0.8 and α=0.05) related to our dichotomous exposure will range from 10 cases per 10,000 person-years (HR=1.03) (for the most frequent exposure and outcome: association of depression with any somatic disease) to 36 cases per 10,000 person-years (HR=1.72) (for the least frequent exposure and outcome: association of other affective disorder with brain tumor). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Register data collection was approved by the Danish Data Protection Agency. According to Danish law, ethical approval and informed consent are not required for purely register-based studies.

2.2. Affective disorder

Mania or bipolar disorder (referred to as bipolar disorder) was identified using the ICD-10 codes F30-31 in the PCR or the NPR. Major depressive disorder (referred to as depression) was identified by ICD-10 codes F32-F33, while other affective disorder was identified by the ICD-10 codes F34, F38, or F39 in the PCR or the NPR. These three conditions were further combined into one single exposure variable termed affective disorder. Number of individuals with the different diagnostic ICD-10 codes at baseline is shown in Supplementary Table 1.

2.3. Somatic disease outcomes

A total of 16 somatic disease outcomes were chosen because they were assumed to share mechanisms with affective disorders, e.g. metabolic dysregulation, inflammatory dysregulation, lifestyle/environmental factors, or brain diseases(Bennett and Thomas, 2014; Berk et al., 2013; Halaris, 2017; Milaneschi et al., 2019), as well as contributing significantly to the disease burden in Denmark(Flachs et al., 2015).

The 16 somatic diseases were classified into three groups: the cardiovascular group comprised ischemic heart disease, stroke, and diabetes; the cancer group comprised lung cancer, colorectal cancer, breast cancer (women), prostate cancer (men), brain tumors (including both malignant and benign tumors), and all other cancers; and the other somatic diseases group comprised COPD, asthma, hip fracture, inflammatory bowel disease, psoriasis, migraine, and dementia.

The somatic disease outcomes were defined using ICD-8 codes before 1995 and ICD-10 codes from January 1st, 1995 onwards in the NPR. Due to few endpoints and relatively specific medication, migraine was identified by a diagnosis in the NPR or by Anatomical Therapeutic Chemical (ATC) classification system codes of prescription migraine medication in the Danish National Prescription Registry. Dementia was the only somatic disease defined by diagnosis in either the LPR or PCR (as it is registered in both). All ICD or ATC codes are provided in Supplementary Table 2.

2.4. Covariates

Based on a review of the literature, we included variables that were associated with affective disorders and somatic disease as potential confounding covariates. Data on age and gender was provided from the Civil Registration System(Pedersen, 2011). Calendar year was categorized as 1995-2001, 2002-2006, 2007-2011, and 2012-2016. Socioeconomic variables included data on highest achieved educational level obtained from the Danish Education Register(Jensen and Rasmussen, 2011) (categorized as primary school only, short, medium, long education and unknown) and marital status from the Civil Registration System (categorized as married, unmarried, divorced, widow/widower and unknown). Medication use was defined as redeemed prescriptions in the Danish National Prescription Registry(Kildemoes et al., 2011) during the last two years before study entry. The National Prescription Registry holds information on all prescriptions redeemed in Danish pharmacies since January 1st, 1995. We included information on somatic medication (statins, non-steroid anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), paracetamol, and anticonception pills in women). All ATC codes are shown in Supplementary Table 2. For further information on the registers included in this study, please see Supplementary Table 3.

2.5. Statistical methods

All analyses were performed in Stata-15 or R. Due to the high completeness of the Danish registers, we had few missing data for marital status (<0.2%) and education (<7.5%). Missing values for categorical variables were included in a specific category classified as “unknown”. Differences in the frequency of somatic diseases present at baseline (disease prevalence) were compared between patients with any affective disorder and the reference population using multivariable adjusted logistic regression models to calculate odds ratios (OR) with 95% confidence intervals (CI).

Time-to-event analyses were calculated with age as the underlying timescale. Individuals were followed from baseline (date of affective diagnosis or January 1st, 1997-2014 [inclusion year] for individuals without affective disorder) until first registration of outcome, emigration, death, affective disorder (for individuals without affective disorder at baseline), or end of follow-up (December 31st, 2018), whichever came first. Prevalent cases at baseline were excluded from the relevant analyses (i.e. prevalent dementia cases were excluded before examining risk of dementia) and, consequently, the population size varied for each disease outcome. Crude incidence rates of somatic diseases were calculated using the stir command in Stata.

The relative risks of somatic diseases in individuals with affective disorder were estimated using Cox proportional hazard regression models to calculate hazard ratios (HR) with 95% CI, while the absolute risks were estimated with the less commonly used Aalen’s additive hazard model(Aalen, 1989). Compared to the proportional hazards model, which estimates hazard ratios, Aalen’s additive hazard model estimates the difference in hazards, that is, the absolute difference in the outcome rate among the exposed versus the non-exposed category. To account for the interdependence of observations in individuals occurring more than once in the dataset (e.g. individuals either selected twice in the reference population or individuals who later received a diagnosis...
of affective disorder), we added a cluster term to all models. In adjusted models, we used different levels of adjustment: 1) age, gender, calendar time, marital status, and education; and 2) with further adjustment for somatic medication within 2 years before baseline, and 3) additional adjustment for psychotropic medication within 2 years before baseline. The proportional hazards assumption was tested graphically by plotting log-minus-log curves and Aalen’s additive hazard assumption of time-constant hazard difference was tested graphically with cumulative coefficient versus time plots.

Finally, all analyses were repeated for the combined group of bipolar disorder, depression, and other affective disorders.

### 3. Results

Among the 246,282 patients with affective disorder, 13,725 (6%) patients had bipolar disorder, 221,903 (90%) had depression, and 10,654 (4%) had another or unspecified affective disorder. This cohort was compared to 167,562 individuals representing a random sample of the background population with no affective disorder at baseline. The distribution of covariates and prevalent diseases at baseline is shown in Table 1 and Supplementary Table 4. Thus, 43.7% of the patients with affective disorder had at least one somatic disease at baseline, while the corresponding number in the background population was 23.6% (Supplementary Table 4). After adjustment for all covariates, affective disorder was still associated with all 16 somatic diseases at baseline with ORs ranging between 1.39 (breast cancer) and 5.71 (dementia) (Supplementary Figure 2). The largest difference in prevalence was seen for dementia (OR 5.71 [95% CI 5.31-6.13]), stroke (OR 2.96 [2.86-3.07]), and lung cancer (OR 2.88 [2.61-3.18]).

The mean follow-up time was 9.5 years (ranged between 0-21 years) and during follow-up, 82,336 individuals developed at least one somatic disease in the cohort of disease-free individuals at baseline (33% of individuals with affective disorder compared to 29% in the reference population). There was an absolute risk difference of developing any somatic disease of 130.6 (95% CI 125.5-135.7) additional cases per 10,000 person-years among patients with affective disorders compared to the reference population, and a corresponding relative risk was 1.50 (95% CI 1.48-1.52) times higher after adjustment for age, gender, socioeconomic status, and medication use. Figs. 1 and 2 show the number of outcomes, absolute risk difference, and HR of developing cardiovascular disease or cancer (Fig. 1) or other somatic diseases (Fig. 2) in patients with different subtypes of affective disorders after multiple adjustments. Crude incidence rate differences are shown in Supplementary Figure 3. In general, the overall patterns of absolute and relative risk estimates were similar. All patients with affective disorder had increased risk of most somatic diseases, except for cancer. Both absolute and relative risk estimates were especially high for dementia with a difference of 37.4 additional cases per 10,000 person-years (35.3-39.4). Hip fracture had 23.7 (21.9-25.5) additional cases, stroke had 27.7 (25.4-30.0), and COPD had 14.9 (12.8-17.0). These differences in absolute risk corresponded to relative risks of (HRMDD 2.85 [95% CI 2.71-2.99]) for dementia, hip fracture (2.07 [1.97-2.17]), COPD (1.43 [1.38-1.49]), and stroke (1.60 [1.54-1.66]), compared to individuals without affective disorder. The risk estimates were slightly lower for patients with bipolar disorder. Both the absolute and relative risks of migraine, ischemic heart disease, diabetes, brain tumors, lung and other cancers, inflammatory bowel disease, asthma, and psoriasis were slightly higher in most patients with affective disorders. Affective disorder was, however, not associated with breast, prostate, or colorectal cancer. There was only a slightly higher risk of lung cancer and other cancers in patients with depression, but not in bipolar disorder patients or patients with other affective disorder. When we examined depression, bipolar and other affective disorders separately, risk estimates tended to be slightly higher in individuals with depression or other affective disorder compared to individuals with bipolar disorder. Important exceptions included risk of brain tumors and psoriasis, for which the risk seemed higher for patients with bipolar disorder. However, due to the low number of endpoints, the confidence intervals were overlapping. Contrarily, bipolar disorder patients had a lower risk of migraine compared to all other individuals.

Estimates based on the group of individuals with any affective

### Table 1

Baseline characteristics of the 246,282 patients with and the 167,562 patients without affective disorder.

<table>
<thead>
<tr>
<th></th>
<th>No affective disorder</th>
<th>Affective disorder</th>
<th>Other affective</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (%)</td>
<td>Bipolar (%)</td>
<td>Depression (%)</td>
</tr>
<tr>
<td>Number, N (%)</td>
<td>167,562 (40.5)</td>
<td>246,282 (59.5)</td>
<td>221,903 (53.6)</td>
</tr>
<tr>
<td>Basic demographic covariables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>47.2 (33.5-61.8)</td>
<td>48.8 (33.3-70.3)</td>
<td>43.8 (31.3-57.3)</td>
</tr>
<tr>
<td>Women, N (%)</td>
<td>84,841 (50.6)</td>
<td>151,595 (61.6)</td>
<td>137,703 (62.1)</td>
</tr>
<tr>
<td>Marital status, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>85,449 (51.0)</td>
<td>93,825 (38.1)</td>
<td>4,664 (34.1)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>53,312 (31.8)</td>
<td>83,244 (33.8)</td>
<td>5,975 (43.5)</td>
</tr>
<tr>
<td>Divorced</td>
<td>16,289 (9.7)</td>
<td>34,012 (13.8)</td>
<td>2,220 (16.2)</td>
</tr>
<tr>
<td>Widow/widower</td>
<td>12,498 (7.5)</td>
<td>35,110 (14.3)</td>
<td>2,258 (16.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (0.0)</td>
<td>91 (0.0)</td>
<td>Microdata</td>
</tr>
<tr>
<td>Education, N (%)</td>
<td></td>
<td></td>
<td>Microdata</td>
</tr>
<tr>
<td>Primary school</td>
<td>53,260 (31.8)</td>
<td>101,052 (41.0)</td>
<td>5,204 (37.9)</td>
</tr>
<tr>
<td>Short education</td>
<td>68,744 (41.0)</td>
<td>82,808 (33.6)</td>
<td>4,756 (34.7)</td>
</tr>
<tr>
<td>Medium education</td>
<td>27,890 (16.6)</td>
<td>31,543 (12.8)</td>
<td>2,157 (15.7)</td>
</tr>
<tr>
<td>Long education</td>
<td>9,472 (5.7)</td>
<td>8,049 (3.3)</td>
<td>683 (5.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8,194 (4.9)</td>
<td>22,830 (9.3)</td>
<td>925 (6.7)</td>
</tr>
<tr>
<td>Medication use (all previous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant medication, N (%)</td>
<td>14,120 (8.4)</td>
<td>166,948 (67.8)</td>
<td>7,790 (56.8)</td>
</tr>
<tr>
<td>Antipsychotic medication, N (%)</td>
<td>3,987 (2.4)</td>
<td>42,549 (17.3)</td>
<td>4,725 (34.4)</td>
</tr>
<tr>
<td>Lithium, N (%)</td>
<td>263 (0.2)</td>
<td>2,061 (0.8)</td>
<td>1,039 (7.6)</td>
</tr>
<tr>
<td>Benzodiazepines, N (%)</td>
<td>11,753 (7.0)</td>
<td>77,504 (31.5)</td>
<td>4,079 (29.7)</td>
</tr>
<tr>
<td>Anticontraception pills, N (%)</td>
<td>18,477 (2.1)</td>
<td>34,176 (22.5)</td>
<td>1,779 (24.6)</td>
</tr>
<tr>
<td>Statin, N (%)</td>
<td>13,225 (7.9)</td>
<td>27,847 (11.3)</td>
<td>968 (7.1)</td>
</tr>
<tr>
<td>NSAI D, N (%)</td>
<td>44,192 (26.4)</td>
<td>92,637 (37.6)</td>
<td>4,326 (31.5)</td>
</tr>
<tr>
<td>Acetylsalicylic acid, N (%)</td>
<td>13,451 (8.0)</td>
<td>38,446 (15.6)</td>
<td>1,117 (8.1)</td>
</tr>
<tr>
<td>Paracetamol, N (%)</td>
<td>16,986 (10.1)</td>
<td>59,314 (24.1)</td>
<td>2,142 (15.6)</td>
</tr>
</tbody>
</table>

IQR=interquartile range. Microdata= one or more of the columns contains microdata (N<5) or allows for calculation of microdata, which, according to the rules of Statistics Denmark, we are not allowed do show due to the protection of personal data.

Only in women. NSAI D=Non-steroidal anti-inflammatory drugs.
disorder are shown in Supplementary Tables 5 and 6 in different models of adjustment. Fig. 3 provides a combined description of the absolute and relative risk estimates for each of the 16 somatic disease outcomes attributed to being diagnosed with any affective disorder. It illustrates that patients with affective disorder had especially increased risk of dementia, followed by stroke, hip fracture, and COPD on both the relative and absolute scale. When comparing the absolute risk estimates to the relative risk estimates, the absolute risk estimates were higher for more frequent diseases such as ischemic heart disease, stroke, COPD, hip fracture, migraine, and dementia, while, as expected, slightly lower for the less frequent diseases such as psoriasis and IBD (Supplementary Figure 4).

4. Discussion

This nationwide cohort study expands the somatic health correlates in patients with different subtypes of affective disorder, providing estimates of both absolute and relative risks of 16 major somatic diseases. On both the absolute and relative scale, patients with affective disorder had especially higher risk of dementia, followed by stroke, hip fracture, and COPD. For most diseases, especially migraine, risk estimates seemed slightly lower among patients with bipolar disorder compared to individuals with depression or other affective disorders. Important exceptions included brain tumors and psoriasis, for which patients with bipolar disorder seemed to have a slightly higher risk. Contrarily,
compared to all other individuals, bipolar disorder patients had lower risk of migraine. When comparing the absolute risk estimates to the relative estimates, the absolute risk estimates were higher for more prevalent diseases such as ischemic heart disease, stroke, COPD, hip fracture, migraine, and dementia, while, as expected, slightly lower for the less prevalent diseases such as psoriasis and IBD (Supplementary Figure 4).

Our study confirmed several previous studies that have reported a higher relative risk of somatic diseases in patients with affective disorder. Recently, a large nationwide exploratory Danish study by Momen et al examined associations between 10 broadly defined mental disorders, including affective disorders and 9 different categories of somatic conditions (Momen et al., 2020). The authors reported a higher relative risk of most somatic conditions except for cancers after a diagnosis of affective disorder with estimates similar to those found in our study. However, our study focused on specific affective disorders and also presented absolute risks of somatic diseases following affective disorder, elucidating the clinical and public health significance. Absolute risk estimates are important and may provide different conclusions than relative risks. As an example, affective disorder was associated with a 28% higher relative risk of inflammatory bowel disease, which was similar to the relative risk for ischemic heart disease (25%). However, due to a lower incidence of inflammatory bowel disease than of ischemic heart disease, the absolute number of additional cases of inflammatory bowel disease attributed to affective disorders was only 2.2 cases per 10,000 person-years compared to 14.7 for ischemic heart disease. In total, patients with affective disorder had 130.6 additional cases of somatic disease per 10,000 person-years. Severe affective disorder affects 100,000 adults in Denmark (Flachs et al., 2015), and according to our risk estimates, these patients will receive 1,300 more somatic disease diagnoses each year compared to individuals without affective disorder. Worldwide, 322 million individuals are estimated to live with depression (World Health Organization, 2017), and, accordingly, these patients will receive more than 4.2 million more diagnoses of somatic diseases.

In our study, we found that the strongest associations on both the absolute and relative scale were seen for dementia and stroke. One hypothesis is that depression through prolonged stress activation and allostatic load might increase the risk of brain diseases due to increased levels of cortisol, catecholamines, and inflammation in the brain (Østergaard et al., 2018). Accordingly, studies have found that depression activates the hypothalamic-pituitary-adrenal axis, leading to increased cortisol, which in turn leads to atrophy of the hippocampus, the latter being associated with cognitive decline (Byers and Yaffe, 2011). The association with other brain diseases may also be explained...
by this perpetual stress response and underlying low-grade inflammation or oxidative stress in the brain (Caneo et al., 2016; SayuriYamagata et al., 2017). We also found relatively strong associations between affective disorder and risk of hip fracture and COPD. This could be mediated by an unhealthy lifestyle including high rates of smoking (Weinberger et al., 2017) and alcohol abuse. However, the relative risk of lung cancer (another smoking-related endpoint) was only moderate, which suggests that smoking alone might not fully explain the findings. Hip fracture risk seemed quite similar to dementia risk, and, accordingly, an association between hip fracture and dementia has previously been reported (Hsu et al., 2018). This may be due to fall induced hip fractures caused by impaired cognition, decreased motor control, and control of affect. Confounding by sleep disturbances could also explain the increased risk of somatic diseases in affective patients. Affective disorders are often accompanied by sleep disturbances and sleep disturbances have been shown to increase risk of especially cardiovascular diseases (Sofi et al., 2014) and dementia (Osorio et al., 2011). This may be due to the circadian disruption, hyperarousal, and increased allostatic load leading to metabolic dysfunction such as altered hypothalamic-pituitary-adrenal axis function and glucose dysregulation (Roth and Roehrs, 2003). Another explanation could be that the association could be mediated by either the use of psychotropic medication or by a lower adherence to somatic treatments. Accordingly, a meta-analysis of 12 studies reported that individuals with depression were three times as likely to be non-adherent to medical treatment as non-depressed individuals (DiMatteo et al., 2000). Finally, other studies have reported a lower utilization of health care services among patients with depression or a lower degree of receiving preventive care (Lord et al., 2010), even despite the tax-financed universal healthcare system in Denmark (Laursen et al., 2009) that might potentially mitigate this tendency somewhat.

Information of the absolute risk of somatic diseases can ensure that clinical practice, treatment and intervention are focused on the somatic diseases where the highest number of cases can be prevented or treated. Our results highlight ischemic heart disease, stroke, COPD, hip fracture, migraine, and dementia as frequent somatic diseases developed in patients with affective disorders. These somatic diseases might to some degree be prevented by addressing modifiable risk factors such as smoking, alcohol, lack of exercise, obesity, unhealthy diet, high blood pressure, high plasma lipids, impaired sleep and risk of falls in elderly patients. (Barnes and Yaffe, 2011; Caldwell et al., 2019; Welte et al., 2015). Our study suggests that screening for risk factors, lifestyle intervention and preventive treatments should routinely be offered to patients with affective disorders. However, lifestyle develops early in life and unhealthy behaviours are related to socioeconomic disadvantage. Thus, interventions in families living in impaired socioeconomic environments should also be considered.

Important strengths of this study include the use of nationwide population-based registers, allowing us to include a large cohort of all patients with a hospital contact for affective disorder between 1997-2014, as well as a random sample of the background population. Tax financed access to health care in Denmark ensured that a population relatively free from selection bias. Furthermore, administrative data from registers do not rely on participant cooperation or accurate recall, which limits potential information bias. Since our population includes all patients diagnosed with affective disorder in Denmark and a relatively large sample of the background population as reference group, we find that our findings have high generalizability. The unique Danish person identification number enabled us to obtain almost complete follow-up information on all somatic outcomes from Danish hospital registers. We also had socioeconomic variables and data on purchase of medication from registers. In this study, we chose to include psychotropic medication status at baseline as a potential confounder because we aimed to explain the biological effect of affective disorders per se. It could be argued that inclusion of these potential confounders in the analyses may lead to over-adjustments because they may also be mediators in the association. However, we also analyzed data in models with lower levels of adjustment (Supplementary Table 4 and 5) with similar, albeit slightly stronger, risk estimates. Furthermore, since affective disorders are often diagnosed in primary care or at private psychiatrists, the cohort of affective patients in this study will include only those with a disease severe enough to be referred to the secondary healthcare system. This might also lead to at least some degree of misclassification among the reference group, which would most likely lead to underestimation of the relationships if mild affective disorders are associated with increased risk of somatic diseases. Additionally, using mainly hospital diagnoses to define somatic disease may lead to some degree of misclassification. This could mean that the absolute risk estimates would be slightly underestimated, especially for outcomes primarily diagnosed in the primary sector, such as diabetes, COPD, asthma, or psoriasis, whereas inclusion of medication may have over-estimated the absolute risk of migraine. Finally, we cannot rule out that...
some of the results are biased by reverse causality. Our study showed that patients with affective disorders had higher prevalence of somatic disease at the time of diagnosis after adjustment for various confounders. This supports studies showing a bidirectional association between affective disorder and somatic disease. Furthermore, as the first registered affective diagnosis in the hospital system occurred quite late in life (25% of patients were older than 70 years), the associations could be explained by reverse causation, i.e. that an underlying, clinically not diagnosed disease increases the risk of getting a diagnosis of affective disorder, even though we did exclude individuals with a previous somatic disease diagnosis. Reverse causation may be caused by diseases that mimic depressive symptoms in older age, such as dementia or brain tumors; undiagnosed diseases either with few clinical symptoms, such as silent stroke; or early-onset diseases diagnosed outside the hospital system, such as inflammatory bowel disease, asthma, psoriasis, or migraine(Cohen et al., 2016). Finally, it can also be argued that the identified increased risk of somatic conditions for patients with affective disorders could be due to Berkson’s bias, that leads to an association because both affective disorders and other somatic diseases increase the likelihood of being admitted to the hospital(Woodfine and Redelmeier, 2015). However, the negative findings for cancer contest this as an explanation of our results.

In conclusion, we found that patients with affective disorder had increased risk of most somatic diseases and that the total burden of somatic disease was 130.6 additional cases per 10,000 person-years. The diseases that contributed most to the disease burden (both relative and absolute burden) were stroke, COPD, hip fracture, and dementia, followed by migraine and ischemic heart disease. From a clinical and public health perspective, effective treatment and intervention are highly needed in patients with affective disorders. Future research should focus on evaluating and explaining the potential mechanisms linking affective disorders and somatic diseases, as well as identify in certain subgroups of affective patients based on their sociodemographic characteristics, lifestyle or clinical profile experience an especially increased risk of somatic disease.

Ethics statement
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Register data collection was approved by the Danish Data Protection Agency. According to Danish law, ethical approval and informed consent are not required for purely register-based studies.

Data availability
Researchers need to apply Statistics Denmark to access the anonymized dataset used in this study. Only aggregated data, where no identification of persons is possible, i.e. minimum five observations in each cell, can be removed from the server containing the data accessed through Statistics Denmark. Thus, we cannot provide an anonymized copy of the dataset as individuals may be identified based on the information in the data, e.g. birthday, sex, date of depression diagnosis, etc. Access to the data through Statistics Denmark is only granted for authorized research and analysis environments of a more permanent nature with a chief researcher and several researchers/analysts. Foreign researchers affiliated with a Danish authorized environment can also get access. Authorizations are granted by the Director General.

Submission declaration
This article has not been published previously, it is not under consideration for publication elsewhere and the publication is approved by all authors.

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CRediT authorship contribution statement

Marie Kim Wium-Andersen: Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Methodology, Writing - original draft. Ida Kim Wium-Andersen: Conceptualization, Methodology, Validation, Writing - review & editing. Terese Sara Høj Jørgensen: Conceptualization, Formal analysis, Methodology, Writing - review & editing. Martin Balslev Jørgensen: Conceptualization, Methodology, Supervision, Validation, Writing - review & editing. Merete Olsen: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest
None.

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Supplementary materials
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