Bidirectional associations between treatment-resistant depression and general medical conditions

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Abstract
Depression is associated with general medical conditions (GMCs), but it is not known if treatment-resistant depression (TRD) affects GMC risk and vice versa. We estimated bidirectional associations between TRD and GMCs (prior and subsequent). All individuals aged 18–69 years, born and living in Denmark, with a first-time prescription for an antidepressant between 2005 and 2012 were identified in the Danish Prescription Registry (N = 154,513). TRD was defined as at least two shifts in treatment regimes. For prior GMCs, we estimated odds ratios...
1. Introduction

Extensive evidence has shown that general medical conditions (GMCs) are associated with an increased risk for developing depression (Egede 2007; Patten 2001) and, vice versa, depression is associated with an increased risk for developing GMCs (Momen et al., 2020; Scott et al., 2016; Tegtehfo et al., 2016). The co-occurrence of depression and GMCs suggests bidirectional associations between the two, further hinting at a shared aetiology. This has been proposed for depression and cardiovascular disorder, chronic obstructive pulmonary disease, rheumatoid arthritis and diabetes type 1 and 2, explained by inflammatory and oxidative / nitrosative stress pathways (Maes et al., 2011; Miller et al., 2009). Despite not knowing what develops first (temporality of events), the co-occurrence of depression with other medical conditions is associated with greater depression symptom severity and GMC severity, decreased treatment adherence and lower remission rates compared to individuals suffering from depression without GMCs (Ishak et al., 2018; Kronish et al., 2006; Moussavi et al., 2007; Rush et al., 2008).

Both depression severity as well as treatment-resistant depression (TRD) influence the complexity of the biderocolocational association between depression and GMCs (Amital et al., 2013; Niles et al., 2015). TRD is broadly defined as the occurrence of an insufficient clinical response to at least two adequate regimes of antidepressants (Gaynes et al., 2019), and has a poor prognosis in terms of increased mortality and disability (Bang Madsen et al., 2020a, Madsen et al., 2020b). As of yet, it is unknown why some people respond to antidepressant treatment and why some people do not, and no specific set of neurobiological markers or genetic profile have proven useful in predicting response or nonresponse (Berlim and Turecki 2007). However, medical conditions related to the immune system and metabolism as well as some types of medications such as immunosuppressants, steroids and sedatives have been considered a potential contributing factor to the occurrence of TRD (Berlim and Turecki 2007; Fagiolini and Kupfer 2003; Keitner et al., 1991). Nevertheless, studies have yielded inconsistent results. Co-morbid depression and hypercholesterolemia has been found to be associated with poor response to antidepressant treatment (Papakostas et al., 2003; Sonawalla et al., 2002), and arthritis and cardiovascular problems to be associated with a worse outcome of depression (Osln et al., 2002). In contrast, a study assessing the effect of GMC comorbidity on response to next-step antidepressant treatments among TRD patients showed that medical conditions were not associated with the likelihood of remission, but the sample included only 97 subjects and medical conditions were examined with a combined score (Perlis et al., 2004). Also, another study found no significant difference between TRD and non-TRD patients with regards to the prevalence of any ICD-10 category of GMCs, this study also included only a relatively limited number of patients (N = 702), limiting statistical power to detect GMCs (Amital et al., 2013).

So far, studies conducted on TRD and medical conditions have mainly been clinical studies based on data sources with insufficient information on the sequence of the events studied, as well as limited sample sizes and follow-up time. As a direct consequence, no studies have been positioned to enlighten the bidirectional association between TRD and GMC and, more importantly, have not answered the overarching questions: i) Do previous medical conditions influence the treatment outcome of a depressive episode and ii) does TRD increase the risk of subsequent medical conditions? To specifically investigate the outlined bidirectional associations, the aim of this study was twofold: first, to examine any potential difference in prior medical conditions between TRD and non-TRD patients and second, to estimate the difference in risk of subsequent medical conditions between those with TRD and non-TRD following their first depressive episode.
(Mors et al., 2011), and the Danish National Patient Register (Lyngé et al., 2011). We identified the study population in the Danish National Prescription Registry, including all individuals born and living in Denmark who filled their first prescription for an antidepressant drug (ATC-code N06A) with the indication “for depression” or “for prevention of depression” (indication codes 168 and 270) aged 18-69 years between January 1, 2005 and December 31, 2012 (N = 175,639).

In order to capture only first-time antidepressant users, a set of four exclusion criteria were applied: 1) Individuals were excluded if they had filled a prescription for a potential add-on medication for depression, including lithium (N05AN01), risperidone (N05AX08), olanzapine (N05AH03), aripiprazole (N05AX12) and quetiapine (N05AH04), before their first prescription for an antidepressant drug (n = 430; 0.2%). 2) Linking each individual to the Danish Psychiatric Central Research Registry and the Danish National Patient Registry, individuals were excluded if they had a hospital in- or outpatient contact before filling their first antidepressant prescription for one of the following disorder categories: Organic, including symptomatic, mental disorders (ICD-10: F00-09, ICD-8: 290.09, 290.10, 290.11, 290.18, 290.19, 292.x9, 293.x9, 294.x9, 309.x9), Schizophrenia, schizotypal and delusional disorders (ICD-10: F20-29, ICD-8: 295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83), and Bipolar disorders (ICD-10: F30-31, ICD-8: 296.19, 296.39, 298.19) (n = 2991; 1.7%) (Pedersen et al., 2014). 3) Individuals were excluded if they had a hospital in- or outpatient contact with a diagnosis of single or recurrent depressive episode (ICD-10: F32, F33, ICD-8: 296.09, 296.29, 298.09, 300.49) more than 30 days prior to their first antidepressant (n = 3374; 1.9%); otherwise they were included in the sample with follow-up beginning on the date of their first prescription. 4) Individuals were excluded if their first treatment regime lasted less than four weeks (n = 14,331; 8.2%). The final study population included 154,513 individuals with depression.

To answer the two aims, two different approaches were used resulting in two different subsets of the population, which are shown in Figure 1 and described in detail in the following.

2.2. Ethics

According to Danish law, informed consent is not required for register-based studies. The Danish Data Protection Agency and the Danish Health Data Authority approved the current study. All data were de-identified and not recognizable at an individual level.

2.3. Definition of treatment-resistant depression

We defined TRD based on the established definition of at least two shifts in treatment regimes, which has been used in recent studies of TRD (Bang Madsen et al., 2020a; Conway et al., 2017; Gaynes et al., 2019; Madsen et al., 2020b). Shifts were identified and defined using three criteria: 1) Shift in medication out of class, e.g. from selective serotonin reuptake inhibitors (SSRI) to serotonin-norepinephrine reuptake inhibitors (SNRI). 2) Augmentation with other psychotropic drugs; lithium, risperidone, olanzapine, aripiprazole and quetiapine or a combination of two different antidepressant drug classes at the same time. 3) In- or outpatient contact with single or recurrent depressive episode. Shifts were only counted if they occurred within the same episode of continuous medical treatment within two years from first antidepressant prescription (Bang Madsen et al., 2020a; Kubitz et al., 2013, Madsen et al., 2020b). Hence, patients were classified as having TRD if they e.g., had two shifts in medication class or one shift in medication class AND augmentation/combination OR a hospital diagnosis of single or recurrent depressive episode. TRD was classified on the date that the criteria were met. For further information, the definition of depressive episode and medication shifts using dispensed prescriptions from The Danish National Prescription Registry have been described in detail elsewhere (Bang Madsen et al., 2020a, Madsen et al., 2020b).

2.4. General medical conditions

Information about GMCs was obtained using criteria based on previous Danish research on coexisting conditions going back to 1995 (the year prescription data became complete) (Momen et al., 2020; Prior et al., 2016). As described in Momen et al., the criteria focus on 31 medical conditions, within nine broad categories: cardiovascular, endocrine, pulmonary, gastrointestinal, urogenital, musculoskeletal, hematologic, neurologic and oncologic conditions (Momen et al., 2020). We identified individuals with GMCs by combining data from three sources: diagnoses made during inpatient admissions and outpatient and emergency visits from the Danish National Patient Registry (Lyngé et al., 2011), prescriptions for disease-specific medications in the Danish National Prescription Registry (Kildehoes et al., 2011), and diagnoses recorded as causes of death in the Danish Register of Causes of Death (only for incident GMCs) (Helweg-Larsen 2011). For example, chronic pulmonary disease was identified by the ICD-10 diagnosis J40–J47 and by prescriptions for obstructive airway disease drugs (ATC code R03). The diagnoses (ICD-10 codes) and drugs (Anatomical Therapeutic Chemical classification system codes) that were included in the definition of each medical condition are provided in Supplementary Table 1. The diagnosis date of the medical condition of interest was the date of first hospital diagnosis, the date of the relevant repeat prescription, or the date of death from the medical condition, whichever occurred first.

2.5. Covariates

Covariates included GMCs other than the GMC of interest and number of other GMCs (0,2,3,4+) defined and categorized as above. Age at first antidepressant prescription was obtained from the Danish National Prescription Registry (Kildehoes et al., 2011) and date of birth, sex and migration status were obtained from the Danish Civil Registration System (Pedersen 2011).
2.6. Statistical analyses

Characteristics of TRD and non-TRD patients were summarized by the use of descriptive statistics.

Prior medical conditions (aim 1): We estimated associations between prior medical conditions and TRD by comparing medical conditions going back to 1995 between TRD cases and a matched reference group of depression patients (non-TRD) (Fig. 1). For each TRD case, five controls were randomly selected from the study population matching on date of birth (+/− 60 days), sex and age at first antidepressant prescription fill (+/− 6 months). Example: a patient was defined treatment-resistant on August 20, 2008, he/she was matched with five patients of same age and sex, who redeemed their first antidepressants on the same date as the case, and who on August 20, 2008 had not become TRD. From this date and backward we look to see if they between 1995 and the index date have had any of the GMCs. Associations were examined using conditional logistic regression models. Models were unadjusted and adjusted for other prior GMCs and number of other prior GMCs and estimates are presented as odds ratios (OR) for each sex.

Subsequent medical conditions (aim 2): To evaluate the association between TRD and subsequent medical conditions, individuals with a prior medical condition of interest were excluded (Fig. 1). We compared incidence rates of a diagnosis of a medical condition according to the presence or absence of TRD using Cox proportional hazards models with age as the underlying time scale. Patients were followed from the date of first antidepressant prescription until emigration, death, the GMC of interest or December 31, 2015, whichever came first. Patients were censored if they, after their first prescription and within two years, had a hospital contact with the ICD-10 diagnoses organic mental disorders (F00-09), schizophrenia, schizotypal and delusional disorders (F20-29), manic episode (F30), and bipolar disorder (F31) on the date of admission. TRD was treated as a time-varying variable, meaning that an individual moved from the unexposed (non-TRD) to the exposed group (TRD) when they fulfilled the requirements for the definition of TRD. Models were adjusted for birth year, age at first antidepressant prescription, other previous GMCs, and number of previous GMCs. Hazard ratios (HR) are presented for each sex.

Statistical analyses were performed in Stata 15.1 (StataCorp, College Station, TX, USA).

3. Results

In the period from 2005 to 2012, 154,513 patients with first-time depression redeemed an antidepressant prescription at ages 18-69 years. Of the total study population, 8294 (5.4%) met the defined criteria for TRD during the follow-up. There were more women in both groups; TRD (60%), non-TRD (58%), and a larger proportion of the TRD group were between 18 and 29 years at the time of their first antidepressant prescription fill compared to non-TRD (37% vs. 26%) and fewer were between 50 and 69 years (21% vs. 31%), Table 1.

The temporal associations of TRD and the nine broad categories of GMCs are shown in Fig. 2. Detailed results for each of the 31 medical conditions are provided in Tables 2 (prior GMCs) and 3 (subsequent GMCs).

3.1. Prior medical conditions occurring before TRD - Women

For women with TRD, the prevalence of musculoskeletal disorders before they became treatment-resistant was larger
Fig. 2 Temporal associations of treatment-resistant depression and nine broad categories of general medical conditions in women and men. To the left is shown the odds for patients with TRD of having had a medical condition before they became treatment-resistant compared with matched non-TRD controls, presented as odds ratios adjusted for other GMCs and number of other GMCs. To the right is shown the risk for patients with TRD of subsequent GMCs compared to all non-TRD patients, presented as hazard ratios adjusted for birthyear, age at first prescription, previous GMCs and number of previous GMCs (patients with prior medical conditions were excluded).

compared to matched non-TRD controls (aOR: 1.35, 95% CI: 1.26-1.46) (Table 2). This was driven by painful conditions (aOR: 1.38, 95% CI: 1.28-1.48) and connective tissue disorder (aOR: 1.23, 95% CI: 1.00-1.51). The prevalence of prior pulmonary disorders was slightly larger (aOR: 1.08, 95% CI: 1.01-1.15) among women with TRD, but the associations of any of the disorders in the category were not significantly increased individually. Larger prevalence of prior neurological disorders (aOR: 1.19, 95% CI: 1.09-1.29) was mainly driven by migraine (aOR: 1.22, 95% CI: 1.09-1.36), while for multiple sclerosis the prevalence was smaller (aOR: 0.46, 95% CI: 0.24-0.88). For endocrine disorders, associations were in opposite directions; diabetes was more prevalent (aOR: 1.23, 95% CI: 1.03-1.46), and thyroid disorder was less prevalent (aOR: 0.87, 95% CI: 0.75-1.00). Prior oncological disorders were more prevalent in non-TRD versus TRD patients (aOR: 0.76, 95% CI: 0.62-0.93).

3.2. Subsequent medical conditions occurring after first medically treated depressive episode - Women

For women with TRD, the risk was increased for subsequent cardiovascular disorders (aHR: 1.43, 95% CI: 1.32-1.54), mainly hypertension (aHR: 1.47, 95% CI: 1.40-1.52) and dyslipidemia (aHR: 1.42, 95% CI: 1.27-1.58); and for endocrine disorders (aHR: 1.52, 95% CI: 1.37-1.67), where the risks of diabetes (aHR: 1.63, 95% CI: 1.42-1.87) and thyroid disorder (aHR: 1.38, 95% CI: 1.21-1.58) were increased (Table 3). The risk of subsequent neurological disorders (aHR: 1.24, 95% CI: 1.13-1.35) was mainly driven by migraine (aHR: 1.22, 95% CI: 1.08-1.39), epilepsy (aHR: 1.70, 95% CI: 1.25-2.30) and neuropathies (aHR: 1.19, 95%CI: 1.03-1.37). In addition, for women with TRD the risk of subsequent pulmonary disorders was slightly increased (aHR. 1.12, 95%
Table 1 Demographic characteristics of TRD and non-TRD patients (N = 154,513).

|                  | TRD  n = 8294 | Non-TRD n = 146,219 |
|------------------|--------------|---------------------|
| Sex              |              |                     |
| Female           | 4938 (60)    | 85,522 (58)         |
| Birthyear        |              |                     |
| 1936–1944        | 345 (4)      | 10,469 (7)          |
| 1945–1954        | 916 (11)     | 24,743 (17)         |
| 1955–1964        | 1414 (17)    | 28,318 (19)         |
| 1965–1974        | 1826 (22)    | 31,934 (22)         |
| 1975–1984        | 1945 (24)    | 29,506 (20)         |
| 1985–1994        | 1848 (22)    | 21,246 (15)         |
| Year of first AD prescription (years) | | |
| 2005–2006        | 1934 (24)    | 36,580 (25)         |
| 2007–2008        | 2077 (25)    | 37,594 (26)         |
| 2009–2010        | 2349 (28)    | 40,620 (28)         |
| 2011–2012        | 1934 (23)    | 31,425 (21)         |
| Age at first AD prescription (years) | | |
| 18–29            | 3044 (37)    | 38,446 (26)         |
| 30–49            | 3495 (42)    | 62,352 (43)         |
| 50–69            | 1755 (21)    | 45,421 (31)         |

CI: 1.02-1.24). Finally, the risk of ulcer/chronic gastritis (aHR: 1.55, 95% CI: 1.22-1.98) and painful condition (aHR: 1.23, 95% CI: 1.15-1.32) was increased.

3.3. Prior medical conditions occurring before TRD - men

For men with TRD, the prevalence of musculoskeletal disorders at the time they became treatment-resistant was larger compared to matched controls (aOR: 1.30, 95% CI: 1.19-1.42), driven by painful conditions (aOR: 1.32, 95% CI: 1.20-1.43) (Table 2). While no association was found for cardiovascular disorders as a category (aOR: 1.00, 95% CI: 0.90-1.12), a negative association was found for peripheral artery occlusion (aOR: 0.64, 95%CI: 0.45-0.92) and stroke (aOR: 0.68, 95% CI: 0.55-0.86). For neurological disorders (aOR: 1.03, 95% CI: 0.92-1.16), the prevalence of migraine (aOR: 1.25, 95% CI: 1.00-1.56) and neuropathies (aOR: 1.27, 95% CI: 1.07-1.52) were larger in men with TRD versus non-TRD.

3.4. Subsequent medical conditions occurring after first medically treated depressive episode - Men

For men with TRD, the risk was increased for cardiovascular disorders (aHR: 1.31, 95% CI: 1.19-1.43), mainly hypertension (aHR: 1.36, 95% CI: 1.22-1.51) and dyslipidemia (aHR: 1.24, 95% CI: 1.10-1.40); and for endocrine disorders (aHR: 1.24, 95% CI: 1.07-1.44), driven by diabetes (aHR: 1.36, 95% CI: 1.15-1.60) (Table 3). The increased risk of musculoskeletal disorders (aHR: 1.48, 95% CI: 1.08-2.04) was due to connective tissue disorder (aHR: 1.95, 95% CI: 1.43-2.65) and painful condition (aHR: 1.12, 95% CI: 1.02-1.22), and the increased risk of hematological disorders (aHR: 1.38, 95% CI: 1.10-1.74) was due to anemias (aHR: 1.39, 95% CI: 1.10-1.77). For neurological disorders (aHR: 1.19, 95% CI: 1.07-1.34), Parkinson’s disease (aHR: 2.15, 95% CI: 1.34-3.43), multiple sclerosis (aHR: 2.07, 95% CI: 1.04-4.13) and hearing problems (aHR: 1.28, 95% CI: 1.03-1.59) were the primary causes.

4. Discussion

To our knowledge, this is the first study to investigate the bidirectional associations between TRD and a broad and comprehensive range of GMCs. We found that for both women and men with TRD the prevalence of prior musculoskeletal disorders (connective tissue disorder in women and painful conditions in both) and migraine before TRD onset was larger than in matched controls with depression. We further found differences between sexes; for women with TRD, prior diabetes was more prevalent and neurological disorders were less prevalent, while for men with TRD, prior neuropathies were more prevalent. For subsequent medical conditions where we explored risk of GMCs after first depressive episode, cardiovascular (hypertension and dyslipidemia), endocrine (diabetes), neurological (mainly epilepsy in women and Parkinson’s disease in men) and musculoskeletal disorders (connective tissue disorder in men and painful condition in both) were increased for both sexes with TRD. In addition, for women with TRD, subsequent chronic pulmonary disease and gastric ulcers were increased, while for men with TRD, increased subsequent hematological disorders (anemias) was found.

The current study is exploratory and offers an overview of the bidirectional associations between TRD and GMCs, and can be used to generate hypotheses for future studies that consider the associations in detail. We do not propose a causal relationship between TRD and medical conditions. The presence of both TRD and a medical condition may be confounded by previous exposures (e.g., childhood abuse, socioeconomic factors, and shared environmental risk factors) or shared genetic factors. However, we speculate that specific explanations for our observations may include several factors related to the metabolism, the immune system, and potential shared genetic vulnerability.

Our observed associations should be considered in light of previous studies suggesting that a poorer outcome and response to treatment characterize depressed patients with concurrent illness irrespective of the coexisting diagnosis. This suggests that any additional burden, rather than the burden caused by specific illness, is the determining factor in predicting a poorer prognosis (Black et al., 1987; Coryell et al., 1985; Keitner et al., 1991). However, other studies suggest that only certain somatic disorders, such as neurological disorders and connective tissue disorders, play a role in the treatment response of depression (Berlim and Turecki 2007; Oslin et al., 2002), which is in accordance with our results.

Cardiovascular problems such as heart disease, hypertension and dyslipidemia have been reported to be accompanied by co-morbid depression and some studies have even found that co-occurring cardiovascular disorders are associated with poor response to antidepressant treatment in pa-
patients with depression (Oslin et al., 2002; Papakostas et al., 2003; Sonawalla et al., 2002). In contrast, we found no associations between TRD and prevalent cardiovascular disorders, which is in line with the study by Amital et al. (2013), but patients with TRD had an increased risk of both subsequent hypertension and dyslipidemia. This finding might suggest that although cardiovascular conditions may not necessarily have an impact on the likelihood to respond to treatment, untreated/insufficiently treated depression might play a role in the occurrence of certain cardiovascular conditions. However, caution should be exercised regarding directionality of this association, because cardiovascular diseases can remain indolent for a prolonged duration before symptoms manifest (Li et al., 2020). Also, given that we restricted on first-time depressive episode, this finding might be due to an effect of age, since the population is relatively young at time of first treatment and cardiovascular conditions have a later onset.

Migraine shares common genetic variant risks with depression (de Boer, van den Maagdenberg, and Terwindt, 2019), and several studies have demonstrated that migraine is often associated with depression (Minen et al., 2016; Oedegaard et al., 2006), and that this may be a bidirectional association (Breslau et al., 1991). We found that for both women and men with TRD, migraine was more prevalent. This is in line with the study by Amital, who found that patients with TRD were more likely to experience prevalent migraine, but the study included a very small sample and the association was not statistically significant (Amital et al., 2013). Evidence suggest that migraineurs who
| Condition                        | WOMEN | MEN     |
|---------------------------------|-------|---------|
|                                 | N of obs | Risktime (years) | n of TRD failures | aHR* | aHR** 95% CI | N of obs | Risktime (years) | n of TRD failures | aHR* | aHR** 95% CI |
| Cardiovascular                  | 70,386 | 439,688 | 720 | 1.51 | (1.32;1.54) | 47,252 | 281,713 | 491 | 1.35 | (1.19;1.43) |
| Hypertension                    | 73,726 | 472,566 | 532 | 1.47 | (1.40;1.52) | 51,868 | 319,49 | 367 | 1.39 | (1.22;1.51) |
| Dyslipidemia                    | 85,531 | 545,613 | 356 | 1.42 | (1.27;1.58) | 55,456 | 339,416 | 281 | 1.26 | (1.10;1.40) |
| Ischemic heart disease          | 88,481 | 603,656 | 80  | 1.11 | (0.84;1.32) | 60,495 | 389,954 | 108 | 1.09 | (0.88;1.29) |
| Atrial fibrillation             | 89,778 | 616,331 | 30  | 0.87 | (0.59;1.23) | 62,632 | 407,671 | 57  | 0.98 | (0.74;1.26) |
| Heart failure                   | 90,071 | 619,584 | 26  | 1.39 | (0.94;2.07) | 63,200 | 412,509 | 38  | 0.98 | (0.69;1.32) |
| Peripheral artery occlusive     | 89,601 | 614,868 | 40  | 1.14 | (0.83;1.56) | 62,865 | 409,266 | 48  | 0.97 | (0.71;1.26) |
| Endocrine                       | 82,670 | 548,338 | 419 | 1.57 | (1.13;1.67) | 59,563 | 381,487 | 186 | 1.33 | (1.07;1.44) |
| Diabetes                        | 87,431 | 593,064 | 218 | 1.75 | (1.42;1.87) | 60,659 | 391,143 | 151 | 1.45 | (1.15;1.60) |
| Thyroid disorder                | 85,345 | 574,311 | 235 | 1.41 | (1.21;1.58) | 63,178 | 411,453 | 41  | 1.19 | (0.84;1.57) |
| Gout                            | NA     | NA      | NA  | NA  | NA            | 63,509 | 415,036 | 14  | 0.81 | (0.43;1.24) |
| Pulmonary                       | 59,809 | 381,377 | 438 | 1.17 | (1.02;1.24) | 48,328 | 299,501 | 253 | 1.07 | (0.92;1.19) |
| Chronic pulmonary disease       | 72,853 | 484,837 | 259 | 1.19 | (1.01;1.30) | 55,821 | 357,450 | 160 | 1.14 | (0.94;1.29) |
| Allergy                         | 70,332 | 458,639 | 368 | 1.15 | (0.98;1.22) | 53,4   | 335,965 | 165 | 0.99 | (0.82;1.12) |
| Gastrointestinal                | 87,369 | 592,700 | 152 | 1.18 | (0.96;1.33) | 60,883 | 392,025 | 147 | 1.23 | (0.99;1.38) |
| Ulcer/chronic gastritis         | 89,329 | 612,094 | 71  | 1.67 | (1.22;1.98) | 62,707 | 408,560 | 56  | 1.40 | (0.99;1.71) |
| Chronic liver disease           | 89,949 | 618,597 | 24  | 1.08 | (0.69;1.59) | 63,187 | 412,385 | 45  | 1.10 | (0.79;1.43) |
| Inflammatory bowel disease      | 89,334 | 613,324 | 38  | 1.19 | (0.82;1.58) | 63,305 | 413,35 | 23  | 1.36 | (0.86;2.00) |

(continued on next page)
Table 3 (continued)

| Condition                        | WOMEN | MEN |
|----------------------------------|-------|-----|
|                                  | N of obs | Risktime (years) | n of TRD failures | aHR* | aHR** 95% Cl | N of obs | Risktime (years) | n of TRD failures | aHR* | aHR** 95% Cl |
| Diverticular disease of intestine| 89,798 | 615,395 | 46 | 1.01 | 0.98 (0.73;1.32) | 63,419 | 412,771 | 48 | 1.13 | 1.09 (0.81;1.45) |
| Urogenital                       | 90,096 | 619,993 | 19 | 1.12 | 1.02 (0.65;1.63) | 61,703 | 397,144 | 104 | 1.03 | 1.02 (0.84;1.24) |
| Chronic kidney disease           | 90,096 | 619,993 | 19 | 1.12 | 1.02 (0.65;1.63) | 63,59 | 415,673 | 29 | 1.18 | 1.11 (0.77;1.62) |
| Prostate disorders               | NA     | NA     | NA | NA | NA | 62,021 | 399,849 | 83 | 0.99 | 0.99 (0.79;1.23) |
| Musculoskeletal                  | 65,190 | 396,952 | 157 | 1.16 | 1.15 (0.93;1.43) | 47,781 | 284,558 | 74 | 1.48 | 1.48 (1.08;2.04) |
| Connective tissue disorder       | 88,544 | 604,017 | 78 | 1.28 | 1.22 (0.97;1.54) | 63,309 | 413,315 | 44 | 2.02 | 1.95 (1.43;2.65) |
| Osteoporosis                     | 88,790 | 604,017 | 87 | 1.04 | 1.03 (0.83;1.28) | 63,602 | 414,580 | 40 | 1.23 | 1.18 (0.86;1.62) |
| Painful condition                | 66,573 | 408,861 | 840 | 1.27 | 1.23 (1.15;1.32) | 48,187 | 287,864 | 475 | 1.13 | 1.12 (1.02;1.22) |
| Hematological                    | 89,224 | 611,281 | 96 | 1.29 | 1.19 (0.97;1.47) | 63,118 | 411,894 | 77 | 1.42 | 1.38 (1.10;1.74) |
| HIV/AIDS                         | NA     | NA     | NA | NA | NA | NA | NA | NA | NA | NA |
| Anemias                          | 89,248 | 611,458 | 96 | 1.29 | 1.19 (0.97;1.46) | 63,241 | 412,925 | 143 | 1.39 | 1.39 (1.10;1.77) |
| Oncological                      | 86,659 | 596,091 | 122 | 1.07 | 1.06 (0.88;1.27) | 61,204 | 403,031 | 104 | 1.01 | 0.99 (0.82;1.21) |
| Neurological                     | 76,858 | 495,416 | 537 | 1.29 | 1.24 (1.13;1.35) | 56,669 | 352,833 | 306 | 1.24 | 1.19 (1.07;1.34) |
| Vision problem                   | 89,375 | 609,747 | 76 | 1.15 | 1.15 (0.91;1.44) | 63,198 | 410,625 | 52 | 1.00 | 0.99 (0.75;1.31) |
| Hearing problem                  | 88,403 | 604,020 | 75 | 1.22 | 1.19 (0.95;1.51) | 61,777 | 399,459 | 87 | 1.29 | 1.28 (1.03;1.59) |
| Migraine                         | 83,462 | 560,191 | 257 | 1.33 | 1.22 (1.08;1.39) | 62,522 | 406,252 | 55 | 1.39 | 1.27 (0.96;1.67) |
| Epilepsy                         | 89,526 | 614,966 | 45 | 1.83 | 1.70 (1.25;2.30) | 63,270 | 412,361 | 39 | 1.24 | 1.18 (0.85;1.62) |
| Parkinson’ s disease             | 90,341 | 622,017 | 7 | 1.85 | 1.85 (0.87;4.00) | 63,872 | 417,661 | 19 | 2.22 | 2.15 (1.34;3.43) |
| Multiple sclerosis               | 89,982 | 619,029 | 16 | 1.18 | 1.13 (0.68;1.87) | 63,770 | 417,459 | 9 | 2.07 | 2.08 (1.04;4.13) |
| Neuropathies                     | 86,982 | 586,562 | 205 | 1.28 | 1.19 (1.03;1.37) | 61,590 | 396,219 | 121 | 1.20 | 1.12 (0.94;1.35) |

NA where there are less than 5 observations or if it is possible to calculate the number in row line based on the numbers in the other rows.

*adjusted for birth year and age at first prescription.

**adjusted for birth year, age at first prescription, other GMCs and number of other GMCs.
suffer from depression are more likely to be refractory to migraine treatments (Minen et al., 2016). Our study suggest that this may also be the case for antidepressant treatment.

Autoinflammatory diseases such as arthritis and diabetes have been associated with a worse outcome of depression (Oslin et al., 2002). As for connective tissue disorder, including arthritis, compared to those with non-TRD, we found that prior diabetes was more prevalent in women with TRD, and for both women and men with TRD the risk of subsequent diabetes was increased. Although certain health behaviors and risk factors partially explain the association of depression and diabetes, mechanisms acting on a cellular level (presence of a proinflammatory state/immune dysregulation) may contribute to this association proposing a shared aetiology (Gibney and Drexhage 2013; Malhi and Mann 2018). TRD has been linked to a state of increased low-grade-inflammation (Arteaga-Henriquez et al., 2019; Benedetti et al., 2017), while the glucose intolerance of type 2 diabetes (the most prevalent form of diabetes) is considered to be due to the state of low-grade-inflammation induced by obesity, more specifically by the increased production of pro-inflammatory cytokines by the adipose tissue (Baldeón et al., 2014). Also, connective tissue disorders are characterized by an increased state of low-grade-inflammation, more speciﬁcally by a state of low-grade-inflammation induced by a high production of type II interferons (IFNs) (Maria et al., 2016). The IFNs not only induce the expression of a multitude of pro-inflammatory compounds, but also the expression of the enzyme IDO-1 affecting the tryptophan catabolism and serotonin levels (Maria et al., 2016).

Several studies have found a higher incidence of a number of medical conditions in patients with depression (Momen et al., 2020; Scott et al., 2016; Tegethoff et al., 2016). Our study adds to the existing knowledge by showing that compared to depression patients, patients with TRD have an increased risk of subsequent diseases related to the cardiovascular, endocrine, pulmonary, musculoskeletal and neurological systems suggesting that poor response to antidepressant treatment might have an influence on the broad spectrum of later GMCs. However, another possibility is that some medical conditions had been present before depression onset, but first diagnosed after depression onset. For instance, the risk of prevalent connective tissue disorder was increased for women with TRD, while for men with TRD only incident connective tissue disorder was increased. For both men and women with TRD the use of analgesics, which is used for musculoskeletal conditions, was increased both before and after depression onset. This might reflect sex differences in help-seeking behavior or differences in onset of depression between men and women. However, it may also be explained by differences in sex hormones, where estrogens are known for their collagen-increasing effect in connective tissue (Chidi-Ogbolu and Baar 2018) and depression-preventive properties (Keyes et al., 2013). Estrogens also regulate basal and stimulated HPA axis activity (Weiser and Handa 2009). The effects of a prolonged high stress state on bodily systems has repeatedly been reported as a confounding factor, increasing both the risk of medical conditions as well as depression (Menke 2019). The mechanisms underlying these effects are slowly unraveled. Just recently, it was found that chronic stress and HPA axis regulation was linked with epigenetic signatures at immune-related genes, thereby providing a possible explanation how aberrant HPA axis function may contribute to heightened inflammation and disease risk (Palma-Gudiel et al., 2020).

4.1. Strengths and limitations

Our study has several strengths, including the large sample size and use of nationwide register data which is collected on a uniform basis and without any loss to follow-up. In addition, the register information allows us to study the temporality of the medical conditions as we have the exact dates for medication use and diagnoses given, which also ensures that there are no problems caused by recall or self-reporting bias. Also, we are able to pick up fatal GMCs, which is not possible in survey studies of GMCs.

The proportion of patients with TRD (5.4%) in our study was similar to what has been reported in US Claims data (6%) (Kubitz et al., 2013) but was smaller than what has recently been reported in register-based Scandinavian studies (13-14%) (Gronemann et al., 2018; Hägg et al., 2020; Reutfors et al., 2018) and international studies (9-20%) (Fife et al., 2017; Li et al., 2019). The main reason for this are the criteria by which the populations are drawn from the registers. The above-mentioned studies investigate populations of patients who were all diagnosed with depression in specialized care. This restriction might be necessary when the indication for the prescription of antidepressants is not available and may increase the validity of the diagnosis (a diagnosis in primary care vs. a diagnosis in specialized psychiatric care). However, the restriction reduces generalizability to the majority of depressive patients who are first treated for depression in primary care (Musliner et al., 2019). Our study included all first-time pharmacologically treated depressive patients, including those who never had contact to specialized care, improving the generalizability to the broader population of individuals with depression. Another reason may be that different TRD definitions were applied in the studies. A recent study by Gronemann et al. examining treatment patterns in patients with a hospital diagnosis of MDD showed that those who switched treatment most often switched within ATC class (to another SSRI or SNRI) (Gronemann et al., 2021). In contrast to the studies by Gronemann et al. and Reutfors et al. we chose not to include medication switches within the same ATC class (e.g. from one SSRI to another SSRI) to avoid misclassifying patients as treatment-resistant when in fact the switch could have been made in response to side effects (Boyce et al., 2020).

A number of limitations should also be acknowledged. In registers, data is primarily collected for administrative purposes and therefore the data does not inform on whether the patients adhere to treatment, whether the treatment reduces depressive symptoms, or the reasons for which the patients shift medication (Taijale and Tiilhonen, 2021). Therefore, we use shifts in treatment trials as a proxy of failed regimes. Similarly, the exact dose of medication was not available in the registers. Instead, we used each patient’s purchase pattern to estimate the individual duration of trials for recording of shifts in medication class as applied
in our previous study (Madsen et al., 2020a) and described in the study by Tanskanen et al. (2014). Further, there are no standard methods for defining TRD, but in our previous studies, we have evaluated our TRD definition by restricting the inclusion of TRD patients and the pattern of associations with outcomes remained robust (Bang Madsen et al., 2020a, Madsen et al., 2020b). We also reduced the possibility that patients with more severe psychopathology were included in our study by excluding individuals with a diagnosis of organic mental disorder, severe mood disorder or schizophrenia before the inception of our study, and censoring individuals who received the diagnoses after start of follow-up. Also, GMC categories comprise a range of diagnoses, and ascertainment of GMCs relies on patients seeking treatment, all of which jointly can limit generalizability to specific disorders in specific populations. In addition, there could be a potential risk for surveillance bias as patients with TRD are followed up more frequently, which subsequently can lead to the detecting of other illnesses. However, in our previous study, we found a higher all-cause mortality in patients with TRD which is in line with our findings that patients with TRD have an increased risk of a broad spectrum of GMC’s (Madsen et al., 2020a). Finally, when using register information, we had no information on potential confounders such as smoking, alcohol consumption, diet, BMI, and physical activity.

Overall, the present study contributes with a broad overview of comorbid medical conditions in patients with TRD and demonstrated that patients with TRD show a distinct pattern of co-occurrence with both prevalent and incident medical conditions compared with non-TRD patients.

Women and men with TRD had higher prevalence of conditions related only to the immune or neurological systems, while the risk of subsequent medical conditions was related to a much broader spectrum of disorders. Future research is needed to determine the exact mechanisms behind the bidirectional associations between TRD and general medical conditions.

Contributors

KBM, TMO and LVP designed the study. KBM, LVP, NM and OPR conducted the analysis and KBM wrote the first draft of the manuscript. OPR, NM, JJMG, BCMH, HD, LVP, PBM and TMO made significant contributions to interpretation of the analysis and writing of the study. All authors share responsibility for the content of the manuscript. The manuscript has been approved by all authors.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2021.04.021.

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