Investigation of early and lifetime clinical features and comorbidities for the risk of developing treatment-resistance depression in a 13-year nationwide cohort study

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Abstract

Background

To investigate the risk of developing treatment-resistant depression among depressive patients by examining clinical features, early prescription patterns, and early and lifetime comorbidities.

Methods

A total of 31,422 depressive inpatients were followed from diagnostic onset to more than ten-years. Treatment-resistant depression was defined by altered antidepressant treatment regimens more than twice or being admitted after received at least two antidepressant treatments. Multiple regression and Cox regression models were used to examine the effects of physical and psychiatric comorbidities, psychosis, and early prescription patterns on the risk of developing treatment-resistant depression.

Results

Female depressive patients (21.24%) were more likely to become treatment-resistant depression than males (14.02%). Early anxiety disorder was commonly observed in the treatment-resistant depression comparing with non-treatment-resistant depression groups (81.48 vs. 58.96%, p < 0.0001). Lifetime anxiety disorder exhibited the highest population attributable fraction (43.1%). 70% of patients with multiple psychiatric comorbidities developed treatment-resistant depression during follow-up. Results in Cox regression further identified that functional gastrointestinal disorders significantly increased the risk of treatment-resistant depression (aHR = 1.18). A higher dose of antidepressants in early disease course exhibited increased risk for treatment-resistant depression (p < 0.0001).

Conclusion

Our findings indicate the need to monitor early comorbidities and polypharmacy patterns in patients with major depressive disorder that are associated with an elevated risk for treatment-resistant depression.

Background

Major depressive disorder (MDD) is a common mental disorder with high lifetime prevalence [1]. The average age of onset for MDD ranges from the patient's early twenties to their late thirties [1]. The symptoms of MDD significantly impair patients' daily functions [1] and a substantial proportion of patients with MDD do not respond to standard antidepressant treatment regimens. Patients that do not respond to antidepressants are said to have treatment-resistant depression (TRD) [2]. Treatment resistance increases medical burden and individual and societal costs [3]. Systematic evaluation of TRD may enhance our understanding of risk profiles, possible mechanisms of disease, prescription patterns, and the potential
impacts on the mental health system. Understanding these factors may help us develop strategies for preventing adverse consequences associated with TRD.

The criteria for TRD has been identified as the failure to benefit from at least two adequate trials of antidepressant treatment with sufficient duration at an adequate dose [4]. The proportion of patients with TRD among patients with MDD varies between studies (ranging from 6–50% according to data-based analyses vs. randomized control studies) due to differences in study designs and definitions of TRD [5–7]. Also, patients with TRD tend to have more frequent inpatient and emergency room (ER) visits [2, 6]. Despite the frequency of treatment failure among MDD patients in clinical settings, few indicators of poor treatment-response have been reported, especially during the early phase of MDD. Several clinical and psychosocial factors were examined for cross-sectional associations with poor treatment response, such as physical and psychiatric comorbidities, bipolarity, and personality traits (e.g., high neuroticism) [6, 8, 9]. There is a lack of information regarding the influence of comorbidities on treatment resistance in different stage of MDD. It is also important to recognize patterns of help-seeking behavior and medical prescriptions during the early stage of MDD to better help TRD patients. Therefore, a prospective study is needed to evaluate the temporal correlation between the risk profile and the special clinical patterns observed before TRD.

Unfortunately, outpatient care is insufficient for many patients with MDD despite advances in clinical care, treatment regimens, and drug development. It has been reported that 8.3% of patients with MDD are hospitalized annually [10]. These patients have more severe symptoms, increased comorbidities, higher suicide risk, and are prescribed higher doses of antidepressant pharmacotherapy [11]. Patients with MDD who are admitted to the hospital may represent a prominent subgroup that requires intense care and complex treatment regimens. Therefore, the prevalence of TRD among inpatients with MDD requires further attention.

We examined a nationwide population sample of inpatients with MDD in Taiwan to investigate the clinical features and medical outcomes of TRD. The use of large-scale claims data with a prospective follow-up that covers the majority of inpatients minimizes selection bias than a clinical trial that evaluates characteristics of TRD. We aimed to identify risk factors and clinical features (e.g., physical factors, psychiatric comorbidities, and psychoses) for TRD. Furthermore, we also evaluated early prescription patterns, medical help-seeking behavior, and the severity of depressive symptoms during the first year of MDD diagnosis for patients who developed TRD versus non-TRD patients during follow-up. The population attributable fraction (PAF) was calculated to identify important comorbid conditions from multivariable regression analyses. The influence of comorbidities on the risk of TRD in different stages of depression was investigated using time-to-event (TRD occurring) analysis during 13 years of follow-up among patients with MDD.

Method

Data source and study population
The national health insurance program was launched in 1995 to finance healthcare for all individuals in Taiwan and covered approximately 97% of the population. The national health insurance research database contains the Psychiatric Inpatients Medical Claim (PIMC) dataset, which includes all patients who were previously hospitalized for any psychiatric diagnosis (n = 187,117). The PIMC dataset includes comprehensive medical records and basic demographic information [12]. Individuals included in the PIMC dataset (n = 39,353) with a principal inpatient diagnosis of MDD between 1996 and 2011 (ICD-9-CM code 296.2-3) were eligible for inclusion in the current study (Fig. 1). Participants were excluded if (1) the MDD diagnosis was not made by a psychiatrist or (2) if they were diagnosed with schizophrenia (ICD-9-CM code 295) or bipolar disorder (BpD) (ICD-9-CM codes 296.0, 296.1, and 296.4-8) before their MDD diagnosis. Taken together, 31,422 inpatients with MDD were included in the current analysis. All patients were followed from the time of the first MDD diagnosis (classified as the first onset of MDD) until December 31, 2011. The longest follow-up duration was 13 years.

**An operational definition of TRD**

Depression is usually classified as TRD when at least two trials of different antidepressants (adequate in terms of dosage and duration) fail to produce a significant clinical improvement. In the present study, we defined participants as treatment-resistant (1) if their antidepressant treatment regimen was altered two or more times [7]; or (2) if they received two or more adequate antidepressant treatment regimens but were subsequently admitted in the psychiatric acute ward due to a major depressive episode. An adequate antidepressant trial was defined as having greater than 56 cumulative defined daily doses (DDD) for each antidepressant treatment over at least eight consecutive weeks [6, 13]. The consecutive period of treatment was calculated with an allowance of discontinuation for seven days, considering that patients were not always able to attend a scheduled outpatient appointment.

**Independent variables and covariates**

Demographic and clinical data between TRD and non-TRD groups were extracted from the PIMC. Demographic features included age, sex, level of urbanization, and income (estimated by insurance). Patient urbanization level was stratified by seven levels with level I being the most urbanized and level VII being the least urbanized [14]. Clinical information included psychiatric and physical comorbidities, prescription patterns, history of seeking medical care, all-cause mortality, conversion rate to another diagnosis, time from the diagnosis of MDD to another diagnosis, and overall utilization of medical care. The following physical comorbidities were examined: diabetes, systemic lupus erythematosus, rheumatoid arthritis, cardiovascular disease, renal disease, functional gastrointestinal disorders (FGIDs), and thyroid dysfunction. Psychiatric comorbidities that were examined included personality disorder, substance use disorder, anxiety disorder, panic disorder, and non-organic psychosis. Overall medical care utilization was extracted to calculate the number of ER visits and admissions to all specialized departments for all participants. The numbers of admissions and outpatient visits for patients diagnosed with MDD were also calculated. Also, a patient with an original diagnosis of MDD may revise to other diagnoses, such as BpD and schizophrenia, during follow-up [8], which might contribute to treatment difficulties using antidepressants. The conversion rate for BpD or schizophrenia was calculated. The all-cause mortality rate
was evaluated since patients with TRD tend to have poor long-term prognosis [15]. The all-cause mortality rate was compared between patients with and without TRD.

Early psychiatric and physical comorbidities were investigated between non-TRD and TRD patients. The definition of early comorbidity with disease referred to patients that had comorbidity one year before or after MDD diagnosis. All comorbidities in the claims database were defined by at least three outpatient visits or one inpatient care visit that was linked to the diagnosis. Furthermore, the severity of depression during the first year following MDD diagnosis was also evaluated. Severe depression was determined by the following criteria: 1) a patient diagnosis matched ICD-9-CM codes: 296.23, 296.24, 296.33 or 296.34; or 2) the patient received an ECT intervention during a depressive episode [16]. Prescription patterns during the first year following the onset of MDD and behavior of seeking medical care one year before or after the onset of depression were also evaluated. The average doses of antidepressants, antipsychotics, and anticonvulsants were evaluated, and any combined treatment regimens (antidepressants and either antipsychotics or anticonvulsants).

**Statistical analysis**

All analyses were performed using SAS, version 9.3. Differences between TRD and non-TRD groups were evaluated using chi-squared tests for categorical variables and *t*-tests for continuous variables. Multivariate Cox regression models were used to examine the effects of demographic variables and clinical features on the risk of developing TRD. The variables that were examined included the following: gender, physical comorbidities, psychiatric comorbidities, diagnosis conversion, the dose of antidepressants following the onset of MDD, and the number of non-psychiatric outpatient visits one year before or after the onset of depression while adjusting for demographic covariates in the model (age, geographic area, urbanization level, and income estimated by insurance). Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for each covariate were reported for regression analyses. PAF for each significant comorbidity was assessed for the presence of TRD using Levin's formula [17].

To evaluate the robustness of the study, two sets of sensitivity analyses were performed. First, we additionally defined consecutive treatment with an allowance of a discontinued period of 3 or 14 days in the sensitivity analysis. Second, the duration of early comorbidity was additionally defined as only before the onset of MDD. There were no significant differences between the different definitions.

Survival analyses (from the onset of MDD to the occurrence of TRD) were performed to evaluate the distribution and proportion of TRD cases stratified by gender, comorbid FGIDs, comorbid thyroid dysfunction, the severity of depressive symptoms within one year of onset, non-organic psychosis, and psychiatric comorbidities (anxiety disorder, substance use disorder, and personality disorder). Individuals who did not develop TRD, died, or dropped out were censored. A two-sided p-value < 0.05 was considered statistically significant.

**Results**
The demographic and clinical characteristics of the patients are presented in Table 1. A total of 11,078 out of 31,422 (35.26%) inpatients with MDD included in the study were defined as having TRD (21.24% of female and 14.02% of male patients). Females accounted for the majority of TRD patients than non-TRD patients (60.24% vs. 39.56%, p<0.001). The age of onset of MDD was higher among the TRD group than the non-TRD group (41.31±15.33 vs. 37.85±18.82, p<0.0001). A greater percentage of patients in the TRD group had no income than the non-TRD group (21.82% vs. 16.3%, p<0.01). Patients with TRD exhibited a higher frequency of physical comorbidities, including diabetes, systemic lupus erythematosus, rheumatoid arthritis, cardiovascular disease, renal disease, FGIDs, and thyroid dysfunction, than non-TRD patients. All psychiatric comorbidities were more prevalent among TRD patients than non-TRD patients; these psychiatric comorbidities included the following conditions: personality disorder (24.34% vs. 15.07%, p<0.0001), substance use disorders (33.03% vs. 16.64%, p<0.0001), anxiety disorder (89.84% vs. 64.70%, p<0.0001), panic disorder (15.63% vs. 6.02%, p<0.0001), and non-organic psychosis (48.02% vs. 32.67%, p<0.0001). During follow-up, a high proportion of patients with TRD had their diagnosis converted to BpD (22.53% vs. 10.57%, p<0.0001) or schizophrenia (9.51% vs. 7.38%, p<0.0001). Patients with TRD utilized medical care more frequently across all specialties than non-TRD patients. Overall medical care utilization was determined by calculating the number of hospital admissions plus ER visits (6.85±15.17 vs. 2.40±4.09, p<0.0001) (Table 1). The average time from the onset of depression to TRD diagnosis was 3.32 years.

The early characteristics of patients with TRD are presented in Table 2. Generally, patients with TRD exhibited greater early physical comorbidities than patients without TRD. For early psychiatric comorbidities, patients with TRD had a higher prevalence of substance use disorder (15.68% vs. 10.58%, p<0.0001), anxiety disorder (81.48% vs. 58.96%, p<0.0001), and panic disorder (6.51% vs. 3.57%, p<0.0001) than patients without TRD. However, patients with TRD had a lower prevalence of early personality disorder (8.34% vs. 10.64%, p<0.0001), early non-organic psychosis (7.23% vs. 11.98%, p<0.0001), and symptoms of severe depression within one year of onset (23.8% vs. 33.97%, p<0.0001). A higher percentage of patients in the TRD group had their diagnosis converted to BpD (13.15% vs. 10.26%, p<0.0001). Among all inpatients with MDD, 22.8% did not receive adequate treatment with antidepressants, antipsychotics, or anticonvulsants for one year since the onset of depression. During the first year of treatment for MDD, patients in the TRD group were prescribed significantly higher doses of antidepressants (279.90 vs. 142.90 DDD, p<0.0001), antipsychotics (26.63 vs. 23.79 DDD, p<0.0001), and anticonvulsants (8.24 vs. 7.26 DDD, p<0.0001) than patients in the non-TRD group, regardless of a TRD diagnosis. Within one year of MDD onset, patients with TRD were also treated more frequently with combined regimens (antidepressants with either antipsychotics or anticonvulsants) than non-TRD patients during the early stage of the disease (16.44% vs. 10.14%, p<0.0001). Patients in the TRD group tended to have more clinic visits than patients in the non-TRD group one year before or after the onset of MDD (psychiatric clinics, mean: 18.87 vs. 11.95, p<0.0001; non-psychiatric clinics, mean: 50.09 vs. 42.31, p<0.0001).

The results of the multivariable Cox regression model are shown in Table 3. The model was adjusted for demographic features including the age of onset, sex, geographic area, urbanization level, and income estimated by insurance. Significant variables included female gender, severe depression, lifetime...
psychiatric comorbidities (anxiety disorder, substance use disorder, personality disorder, and non-organic psychosis), lifetime physical comorbidities (diabetes, FGIDs, and thyroid dysfunction), conversion of the diagnosis to BpD, the daily dosage of antidepressants within one year of onset, and non-psychiatric outpatient visits one year before or after the onset of depression. Anxiety disorder exhibited the strongest effect associated with TRD (aHR=2.03, 95% CI: 1.90–2.17), followed by conversion of the diagnosis to BpD (aHR=1.72, 95% CI: 1.65–1.79), substance use disorder (aHR=1.43, 95% CI: 1.38–1.49), female gender (aHR=1.23, 95% CI: 1.18–1.28), and personality disorder (aHR=1.23, 95% CI: 1.17–1.29). The PAF of each comorbidity for TRD was calculated using aHR from the multivariable Cox regression model. The most common PAFs were as follows: lifetime anxiety disorder (43.11%), severe depression (11.00%), substance use disorder (8.79%), non-organic psychosis (7.08%), and FGIDs (5.37%). The average daily dose of antidepressants within one year since the onset of MDD (aHR=1.003, 95% CI: 1.003–1.003) and the number of non-psychiatric outpatient visits one year before or after the onset of depression (aHR=1.001, 95% CI: 1.001–1.002) were also significantly associated with an increased risk of TRD.

The results of the survival analyses are shown in Figure 2. A significant gender difference was identified between groups (p<0.0001). Physical comorbidities, including FGIDs and thyroid dysfunction, were associated with a higher frequency of TRD diagnosis during follow-up (p<0.0001). Surprisingly, patients with early severe depressive symptoms had better prognosis than those without early severe symptoms (p<0.0001). The survival rate was significantly reduced in patients with more than one comorbid psychiatric condition. The 10-year survival rate was approximately 31% among patients with multiple psychiatric comorbidities (anxiety disorder, substance use disorder, and personality disorder) than 85% among patients with no prior psychiatric comorbidities.

Discussion

According to this nationwide study, one out of three MDD inpatients has TRD. Furthermore, the results showed that patients with multiple psychiatric comorbidities have a lower 10-year survival rate than patients without these conditions (31% vs. 85%). The large registry claims that data-based studies are less likely to suffer from recall bias since the registration rate is high (97%) and all data regarding prescribed medications are documented. This type of study is especially beneficial when long-term clinical management is recorded, including the duration of depressive episodes within a pre-specified patient population and clinical characteristics (comorbid conditions) [6, 18]. However, claims data may not include the assessment of treatment response, and a poor response to medication may be underestimated. The definition of TRD in the current study was adapted from a previous study of claims data and was determined based on whether the patient's antidepressant treatment regimen was altered two or more times [5–7]. However, some patients who continued taking medication still suffered from depression. To complement the criteria of altering medication, this definition was further added: if the patient received two or more adequate antidepressant treatment regimens but was subsequently admitted in a psychiatric acute ward. This amended definition may represent a useful proxy to capture treatment failure and allow for better identifying TRD among patients who remain in clinical settings [7, 19, 20].
The current study identified the female gender as a risk factor for TRD (aHR = 1.23). A cross-sectional study in the UK that used questionnaires to collect treatment history found that 70% of patients with TRD were female [20], which is consistent with our findings. Furthermore, increased vulnerability for depression in women begins at puberty and declines after menopause [21]. One possible explanation is that the hypothalamic–pituitary–adrenal function (cortisol levels) is more likely to fluctuate in response to stressors and during depressive episodes among women [22]. A redox imbalance elicited by estrogen has been shown to weaken the enzymatic antioxidant defense, which may be linked with TRD [23, 24]. While several physical comorbidities increased the risk of depression [25], it is unknown whether these comorbidities increased the risk of TRD. The current study showed that patients with TRD had more physical comorbidities than non-TRD patients during long-term follow-up, including diabetes, FGIDs, and thyroid dysfunction. Also, patients with prior FGIDs or thyroid dysfunction had an increased risk of developing TRD. Growing evidence suggests a bidirectional communication between the gut and brain [26]. An unhealthy gut may cause treatment complications and reduce responsiveness to antidepressant treatment. Other studies show that antidepressants may be used for treating FGIDs [27]. Previous studies have also indicated that thyroid dysfunction, which is more prevalent among women, may also influence treatment outcomes [23, 28]. The aHR among these physical comorbidities ranges from 1.08 (diabetes mellitus) to 1.18 (FGIDs). Taken together, these risk factors have a mild impact on the development of TRD and therefore warrant further study.

The current study reports that long-term psychiatric comorbidities are important risk factors for developing TRD. In a previous study, anxiety disorders, particularly panic disorder, are associated with TRD [29]. One Japanese study demonstrated that certain personality traits, such as low cooperativeness and high neuroticism, are positively correlated with TRD [9]. We report a 2.03-fold higher risk of developing TRD among patients with a comorbid anxiety disorder. Substance use disorder is also a risk factor for TRD (aHR = 1.43). Previous studies have reported cross-sectional correlations between comorbidities and TRD without considering the temporal relationships [6, 8, 9]. The Cox regression and survival analyses demonstrated that the temporal relationship between long-term psychiatric comorbidities significantly increased the risk of subsequent treatment resistance. In general, the aHR for psychiatric comorbidities is higher than physical comorbidities. Furthermore, around 70% of patients with multiple psychiatric comorbidities developed TRD in our study. In subsequent analyses of psychiatric comorbidities during the early stages of the disease, including non-organic psychosis, personality disorder, and severe depression, the occurrence of TRD was not higher, which seemed to be different from lifetime psychiatric comorbidities. One possible explanation for these results is that patients with initial severe and psychotic depression may have been treated more thoroughly or prescribed a higher dose of antidepressant medication. It should be noted that persistent psychiatric comorbidities would eventually increase the risk of TRD. Taken together, these comorbidity profiles for TRD are important and they warrant further evaluation for the early detection of TRD.

In a clinical study, Hamilton reported that somatic symptoms prevailed among a great majority of depressed patients and they may initially seek non-psychiatric medical care before psychiatric care [30]. Another study indicated that 65% of patients with depression sought help in the general medical care prior
to psychiatric clinic [31]. In the current study, patients in the TRD group visited non-psychiatric clinics more than patients in the non-TRD group. Patients in the TRD group also visited non-psychiatric clinics more than psychiatric clinics during their first year of treatment. Patients with depression may delay the proper treatment, which may correlate with treatment resistance. Therefore, it is important to evaluate these patients with depression who visited non-psychiatric clinics early on and provide suitable treatment for them.

In the current study, patients in the TRD group had significantly higher doses of psychotropic prescriptions and a greater incidence of long-term use than patients in the non-TRD group within one year of the MDD diagnosis. The dosage of antidepressants was also statistically associated with TRD after adjusting for multivariables. Long-term treatment with antidepressants might have contributed to subsequent treatment resistance [32]. There are some possible explanations for this phenomenon. Firstly, treating patients with mood disorders using antidepressants may have paradoxical effect (exacerbate depression) [33, 34]. Secondly, previous studies have described antidepressant-induced switching and cycle acceleration among patients with bipolar disorder [35]. In the current study, patients whose diagnosis was converted to BpD experienced a 1.72-fold higher risk of developing TRD. Thirdly, tolerance to antidepressants has been reported [36]. Patients with TRD also had more complex treatment regimens, since it is a common strategy to use higher doses and adjunctive psychotropics to counter poor response to medication [37]. A recent meta-analysis of placebo-controlled trials demonstrated that adjunctive antipsychotics were effective for the treatment of TRD [38]. However, since the current study was not a randomized, placebo-controlled trial, we did not compare a combined treatment regimen with monotherapy. Rather, we aimed to identify those patients that may require early attention and more complex treatment. Another meta-analysis demonstrated the efficacy of lithium augmentation with antidepressants compared with the placebo [39]. The results of the current study suggest that early prescription patterns in patients may represent a proxy for a combined treatment regimen and poor response/prognosis.

This study has several limitations that need to be considered when interpreting the results. Firstly, structured interview data was not available since we relied solely on claims data. Furthermore, more detailed clinical features and the assessments of disease severity were not available. Secondly, we do not have information on uninsured subjects. However, this study is highly representative of the target population since approximately 97% of the population was insured. Thirdly, it was not possible to evaluate patients’ treatment compliance. Nevertheless, we attempted to exclude those with poor compliance (e.g., patients filling prescriptions for less than 56 days). Fourthly, we intended to investigate the early features of the TRD group, but we did not have information on the subjects before they sought medical help. Fifthly, we did not consider the patient's lifestyle and personal history (i.e., coping strategies, exercise habits, smoking, psychological trauma, etc.) which might have influenced the incidence of TRD. Finally, the mortality rate may be underestimated since death records were missing from the dataset and we cannot clarify the primary causes of death. Thus, future studies are needed to link this database with national death records to answer such questions.

Conclusions
At least one of three inpatients with MDD developed TRD according to this study. These patients visited non-psychiatric medical care more frequently than specialized psychiatric facilities and they were prescribed higher doses of psychotropic agents within the first year of a MDD diagnosis. Also, patients with TRD had lower incomes and utilized medical services more frequently than patients without TRD. Also, female patients exhibited a higher risk for TRD than male patients. Our findings indicated that physical and psychiatric comorbidity patterns substantially increase the risk of TRD during follow-up, and 70% of patients with multiple psychiatric comorbidities developed TRD. Clinicians should be more aware of patients’ physical and psychiatric comorbidity patterns and polypharmacy to better develop comprehensive treatment plans and minimize the risk of TRD.

**Abbreviations**

TRD: Treatment-resistant depression; MDD: Major depressive disorder; ER: Emergency room; PAF: Population attributable fraction; PIMC: Psychiatric Inpatients Medical Claim; BpD: Bipolar disorder; DDD: Defined daily doses; FGIDs: Functional gastrointestinal disorders; aHRs: Adjusted hazard ratios

**Declarations**

**Ethics approval and consent to participate**

The study received ethical approval from the Institutional Review Board (IRB) of National Taiwan University (NTUH-REC-201303020RINC).

**Consent for publication**

Not applicable. This study use unidentifiable data.

**Availability of data and materials**

The datasets generated and/or analyzed of the current study are not publicly available due to the privacy policy of statistics department of Ministry of Health and Welfare, Taiwan.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contribution**
Study concept and design: SSH, PHK, HHC, WJC; Acquisition of data: SSH, JW; Analysis and interpretation of data: SSH, PHK, HCC; Drafting of the manuscript: SSH, PHK, HHC; Critical revision of the manuscript: SSH, PHK, HHC.

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Tables
Table 1. Lifetime demographic and clinical characteristics between non-TRD and TRD patients (N=31,422)

| Variable                                      | non-TRD group (N=20,344) | %      | TRD group (N=11,078) | %      |
|-----------------------------------------------|--------------------------|--------|----------------------|--------|
| Female*                                       | 8048                     | 39.56  | 6673                 | 60.2c  |
| Urbanization level residence¹                 |                          |        |                      |        |
| I–III                                         | 16188                    | 79.61  | 8985                 | 81.1c  |
| IV–VII                                        | 4147                     | 20.4   | 2092                 | 18.8c  |
| Estimated income by insurance (no income)*    |                          |        |                      |        |
| All-cause mortality                           |                          |        |                      |        |
| Lifetime physical comorbidity                 |                          |        |                      |        |
| Diabetes mellitus*                            | 3183                     | 15.65  | 2690                 | 24.2f  |
| Systemic lupus erythematosus*                 | 95                       | 0.47   | 113                  | 1.0h   |
| Rheumatoid arthritis*                         | 308                      | 1.51   | 356                  | 3.2i   |
| Cardiovascular disease*                       | 3607                     | 17.73  | 2805                 | 25.3j  |
| Renal disease*                                | 1829                     | 8.99   | 1330                 | 12.0k  |
| Functional gastrointestinal disorders*         | 5250                     | 25.81  | 4660                 | 42.0l  |
| Thyroid dysfunction*                          | 922                      | 4.53   | 1058                 | 9.5m   |
| Lifetime psychiatric comorbidity              |                          |        |                      |        |
| Personality disorder*                         | 3065                     | 15.07  | 2696                 | 24.3n  |
| Substance use disorder*                       | 3385                     | 16.64  | 3659                 | 33.0o  |
| Anxiety disorder*                             | 13163                    | 64.7   | 9952                 | 89.8p  |
| Panic disorder*                               | 1224                     | 6.02   | 1732                 | 15.6q  |
| Non-organic psychosis*                        | 6646                     | 32.67  | 5320                 | 48.0r  |
| Severe depression*                            | 9338                     | 45.90  | 6836                 | 61.7s  |
| Converted diagnosis to bipolar disorder*      | 2150                     | 10.57  | 2496                 | 22.5t  |
| Converted diagnosis to schizophrenia *        | 1502                     | 7.38   | 1053                 | 9.5u   |

| Mean  | SD    | Mean  | SD    |
|-------|-------|-------|-------|
| Age of onset for depression*                  | 37.85 | 18.82 | 41.31 | 15.3v |
| Age of onset for                                | ...   | ...   | 44.62 | 15.6w |
|                                | 1.43  | 1.79  | 3.50  | 4.6f |
|--------------------------------|-------|-------|-------|------|
| Numbers of lifetime admissions for major depression* | 18.68 | 31.28 | 73.29 | 71.5f |
| Overall medical care utilization for all subspecialties* | 2.40  | 4.09  | 6.85  | 15.1f |
| Days from depression to bipolar disorder | 1154.95 | 1080.22 | 1704.64 | 1125.9f |
| Days from depression to TRD | ...   | ...   | 1211.53 | 1004.6f |

*: p-value<0.0001.

Abbreviations: TRD, treatment-resistant depression

Note 1. Seven levels, with one being the most urbanized and seven being the least urbanized

Note 2. Overall medical care utilization represented numbers of admissions and emergency room visits
Table 2. Early comorbidities, prescription pattern, and behavior of seeking medical care between non-TRD and TRD patients (N=31,422)

| Variable                                                                 | non-TRD group | TRD group |
|-------------------------------------------------------------------------|---------------|-----------|
|                                                                         | (N=20,344)    | (N=11,078) |
|                                                                         | %             | %         |
| Early physical comorbidity                                            |               |           |
| Diabetes mellitus*                                                      | 2182          | 1459      |
|                                                                           | 10.73         | 13.1%     |
| Systemic lupus erythematosus*                                           | 60            | 63        |
|                                                                           | 0.29          | 0.5%      |
| Rheumatoid arthritis                                                    | 178           | 135       |
|                                                                           | 0.87          | 1.2%      |
| Cardiac vascular disease*                                               | 4070          | 2718      |
|                                                                           | 20.01         | 24.5%     |
| Renal disease                                                           | 2689          | 1773      |
|                                                                           | 13.22         | 16%       |
| Functional gastrointestinal disorders*                                   | 3639          | 2682      |
|                                                                           | 17.89         | 24.2%     |
| Thyroid dysfunction*                                                    | 556           | 515       |
|                                                                           | 2.73          | 4.6%      |
| Atopic dermatitis                                                       | 406           | 226       |
|                                                                           | 2            | 2.0%      |
| Early psychiatric comorbidity                                           |               |           |
| Personality disorder*                                                   | 2164          | 924       |
|                                                                           | 10.64         | 8.3%      |
| Substance using disorder*                                               | 2153          | 1737      |
|                                                                           | 10.58         | 15.6%     |
| Anxiety disorder*                                                       | 11994         | 9026      |
|                                                                           | 58.96         | 81.4%     |
| Panic disorder*                                                         | 727           | 721       |
|                                                                           | 3.57          | 6.5%      |
| Non-organic psychosis*                                                  | 2438          | 801       |
|                                                                           | 11.98         | 7.2%      |
| Converted diagnosis to BpD within one year of onset*                    | 2087          | 1457      |
|                                                                           | 10.26         | 13.1%     |
| Severe depression within one year of onset*                             | 6910          | 2637      |
|                                                                           | 33.97         | 23.8%     |
| Prescription pattern within one year of onset                           |               |           |
| Antidepressants plus antipsychotics or anticonvulsants *                | 2062          | 1821      |
|                                                                           | 10.14         | 16.4%     |
| Mean Dosage of antidepre                                                | 142.90        | 279.90    |
| SD                                                                      | 152.90        | 223.41    |

* Denotes statistical significance.
|                           | 7.26 | 34.02 | 8.24 | 34.1¢ |
|---------------------------|------|-------|------|-------|
| Dosage of anticonvulsants |      |       |      |       |
| (DDD)*                    |      |       |      |       |
| Dosage of antipsychotics  | 23.79| 61.72 | 26.63| 64.0¢|
| (DDD)*                    |      |       |      |       |
| Behavior of help-seeking  |      |       |      |       |
| for psychiatric medical   |      |       |      |       |
| care²                     |      |       |      |       |
| Numbers of outpatient     | 11.95| 9.75  | 18.87| 13.7¢|
| visits*                   |      |       |      |       |
| Behavior of help-seeking  |      |       |      |       |
| for non-psychiatric       |      |       |      |       |
| medical care              |      |       |      |       |
| Numbers of outpatient     | 42.31| 41.36 | 50.09| 50.0¢|
| visits*                   |      |       |      |       |
| Numbers of different      | 15.80| 10.68 | 19.15| 11.7¢|
| physicians that patients  |      |       |      |       |
| visited*                  |      |       |      |       |

*: p-value<0.0001, #: p-value <0.01

Abbreviations: TRD, treatment-resistant depression; BpD, bipolar disorder; DDD, defined daily dose.

Note: 1. Patients had comorbidity before depression onset or within one year after onset of depression

Note: 2. Duration was within one year prior or after onset of depression
### Table 3. Multivariable Cox regression\(^1\) analysis for risk of treatment-resistant depression

| Variable                                                                 | aHR    | 95% CI     | PAF     |
|--------------------------------------------------------------------------|--------|------------|---------|
| **Age of onset (depression) ***                                          | 0.0058 | 0.0044     | 0.0071  |
| **Female**                                                               | 1.23   | 1.18       | 1.28    |
| **Lifetime physical comorbidities**                                     |        |            |         |
| Diabetes mellitus                                                          | 1.08   | 1.03       | 1.13    | 1.47%  |
| Coronary artery disease                                                   | 0.92   | 0.87       | 0.97    |
| Renal disease                                                             | 0.96   | 0.90       | 1.02    |
| **Functional gastrointestinal disorders**                                | 1.18   | 1.13       | 1.23    | 5.37%  |
| **Thyroid dysfunction**                                                  | 1.13   | 1.06       | 1.20    | 0.81%  |
| **Lifetime psychiatric comorbidities**                                   |        |            |         |
| Personality disorder                                                      | 1.23   | 1.17       | 1.29    | 4.05%  |
| Substance use disorder                                                   | 1.43   | 1.38       | 1.49    | 8.79%  |
| Anxiety disorder                                                          | 2.03   | 1.90       | 2.17    | 43.11% |
| Non-organic psychosis                                                    | 1.20   | 1.14       | 1.25    | 7.08%  |
| Severe depression                                                         | 1.24   | 1.18       | 1.30    | 11%    |
| Converting diagnosis to bipolar disorder*                                 | 1.72   | 1.65       | 1.79    |
| **Prescription pattern within one year of onset**                        |        |            |         |
| Dosage of antidepressants (defined daily dose)*                           | 1.003  | 1.003      | 1.003   |
| Numbers of non-psychiatric outpatient visits within one year prior or after onset of depression* | 1.001  | 1.001      | 1.002   |

*: p-value<0.0001, &: p-value<0.001, #: p-value<0.01

Abbreviations: CI, Confidence Interval; PAF, population attributable fraction; aHR, adjusted hazard ratio
Note 1. Model adjusted for demographic features including geographic area, urbanization level, and income estimated by insurance

Figures

**Figure 1**

Consort diagram of participants' selection. Abbreviations: TRD, treatment-resistant depression; MDD, major depressive disorder
Figure 2

Survival curves of TRD in different models. 2a) for gender; 2b) for functional gastrointestinal disorder; 2c) for thyroid dysfunction; 2d) for severe depression within 1st year since onset; 2e) for non-organic psychosis; 2f) for different psychiatric comorbidities.