# Risk Factors for Suicide and Suicide Attempts Among Patients With Treatment-Resistant Depression: Nested Case-Control Study

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Published online: 27 Nov 2019.

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# Risk Factors for Suicide and Suicide Attempts Among Patients With Treatment-Resistant Depression: Nested Case-Control Study

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*The risk of suicide is elevated among patients with treatment-resistant depression (TRD). Risk factors for suicide and suicide attempts among cases and controls with TRD were investigated using data from nationwide Swedish registers. Among 119,407 antidepressant initiators with a diagnosis of depression, 15,631 patients who started a third sequential treatment trial during the same depressive episode were classified with TRD. A nested case-control study compared cases with suicide and suicide attempts with up to three closely matched controls. Sociodemographic and clinical risk factors were assessed using conditional logistic regression analyses. In all, 178 patients died by suicide and 1,242 experienced a suicide attempt during follow-up. History of suicide attempts, especially if <1 year after the attempt, was a significant independent risk factor for suicide (adjusted odds ratio [aOR], 8.9; 95% confidence interval [CI], 5.1–15.7) as were 10 to 12 years of education compared to lower education (aOR, 1.69; 95% CI, 1.02–2.81). For attempted suicide, the strongest independent risk factors were history of suicide attempts (<1 year aOR, 5.1; 95% CI, 4.0–6.5), substance abuse (aOR, 2.6; 95% CI, 2.2–3.1), personality disorders (aOR, 1.9; 95% CI, 1.5–2.3), and somatic comorbidity (aOR, 2.0; 95% CI, 1.04–3.9). Suicide attempts, especially if recent, are strong risk factors for completed suicide among patients with TRD. Established risk factors for suicide attempts were confirmed for patients with TRD.*

**Keywords**  depressive disorder, treatment-resistant, suicide, attempted, epidemiology

## BACKGROUND

Almost 1 million people worldwide, including more than 150,000 people in the Organisation for Economic Co-operation and Development (OECD) countries, die by suicide each year, with vast consequences for global public health (World Health Organization 2014; OECD, 2013). More than 90% of suicides have been linked to a mental disorder, most commonly major depressive disorder (MDD; Cavanagh, Carson, Sharpe, & Lawrie, 2003). The risk increase among patients with MDD is 15-fold, and among all patients with affective disorders, the number of patients who are estimated to die by suicide is 2 to 9% (Bostwick & Pankratz, 2000; Crump, Sundquist, Sundquist, & Winkleby, 2014). In addition to having psychiatric disorders, several other risk factors for suicide and suicide attempts have been identified. While suicide attempts are more common in younger ages and among women, the risk for completed suicide is, in most countries, higher in elder patients and among men (Crump et al., 2014; Turecki & Brent, 2016). Chronic somatic illness, such as chronic obstructive pulmonary disease, cancer, spine disorders, asthma, and stroke, increases the risk of suicide (Crump et al., 2014). Other established sociodemographic risk factors for both suicide and suicide attempts include living alone and, among men, low education and income (Crump et al., 2014; Turecki & Brent, 2016).

The issue of MDD being a strong risk factor for suicide is further complicated by the fact that a large proportion of patients have depression that typically does not respond to the standard treatments available today. The term treatment-resistant depression (TRD) has been used increasingly over the last decades and usually translates into MDD in which the patient's condition has not responded to two or more adequate treatment trials (Conway, George, & Sackeim, 2017; Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012). Depending on whether response or remission of symptoms is used in the definition of TRD, the proportion among patients with MDD meeting these criteria ranged between 35% and 64% in the large clinical data sets from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study and the European Group for the Study of Resistant Depression samples (Kautzky et al., 2019; Rush, Trivedi, Wisniewski, Nierenberg et al., 2006, 2006; Souery et al., 2007). Despite this, studies with long-term follow-up of patients with TRD are scarce and do not include risk factor analyses of adverse outcomes such as death or suicide (Dunner et al., 2006; Fekadu et al., 2009).

From a research methodology perspective, suicide is a rare outcome, and its risk factors in different populations may be difficult to study in a clinical setting (Aaronson et al., 2017). Hence, observational register studies may be helpful, but this methodology offers challenges of its own. For example, the administrative data must contain information of deaths and their causes, records of suicide attempts, as well as data on MDD diagnosis and treatment trials during a sufficient follow-up time in order to identify patients with TRD. As a proxy for identifying treatment resistance, the method of using prescription data in modeling TRD has been increasingly used in register studies

(Corey-Lisle, Birnbaum, Greenberg, Marynchenko, & Claxton, 2002; Fife et al., 2017; Gronemann, Jorgensen, Nordentoft, Andersen, & Osler, 2018; Reutfors et al., 2018; Thomas et al., 2013). In these studies, the rate of TRD among antidepressant initiators has consistently been lower compared to in clinical studies, ranging from 12 to 20%.

In a recent study, we investigated mortality among patients with TRD in a large register-based cohort of Swedish patients with MDD and found that the risk of death from external causes, including suicide, was almost doubled among the patients defined as having TRD (Reutfors et al., 2018). Thus, investigating potential risk factors for both suicide and suicide attempts in this particular group seems a priority. The aim of this study was to examine several potential risk factors for suicide and suicide attempts among patients with TRD identified in Swedish national registers.

## METHODS

### Source Study Population

All residents in Sweden 18 to 69 years old who in 2006 to 2014 were diagnosed with depression in specialized care (ICD-10 F32-34) and who had been dispensed an antidepressant (Anatomical Therapeutic Chemical [ATC] code N06A) were identified using the Swedish National Patient Register (NPR; Ludvigsson et al., 2011) and the Prescribed Drug Register (PDR; Wettermark et al., 2007), held by the Swedish Social Insurance Agency. The NPR contains all ICD-10 diagnoses and procedure codes registered in Swedish specialized care, with nationwide inpatient and outpatient coverage from 2001

onward. The PDR contains data on all dispensed prescriptions in Swedish pharmacies from July 1, 2005. In order to capture incident cases of antidepressant treatment, a preceding 180-day washout period with no dispensed antidepressant prescriptions or treatment with electroconvulsive therapy (ECT) or repeated transcranial magnetic stimulation (rTMS) was required for inclusion. Additional exclusion criteria were any occurrence of diagnoses of bipolar or psychotic disorders or dementia, or prescriptions of antipsychotics, lithium, valproate, carbamazepine and lamotrigine before the first antidepressant prescription. Linkage between registers was made through the 10-digit personal number assigned to all Swedish residents (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009). This yielded an MDD initiator cohort of 119,407 patients at baseline.

### Definition of TRD

Patients in the cohort were followed prospectively and were classified with TRD if the definitions of at least two adequate, differing treatment trials were met and a third one was commenced. An adequate treatment trial was defined as prescriptions of antidepressants, and/or (from the second trial) augmentation therapy with antipsychotics or mood stabilizers, or a course of ECT/rTMS, lasting for at least 28 days according to package sizes, semi-manually read dosage text instructions, or registered procedure codes for ECT/rTMS. Treatment gaps of more than 28 days were not allowed in order to emulate sequential treatment; these patients were excluded but, after a new 180-day washout period, again available for cohort inclusion. Antidepressant switches could be within the same class

(e.g., from one selective serotonin reuptake inhibitor [SSRI] to another) or between classes (e.g., from an SSRI to a tricyclic antidepressant).

## Cases and Controls

Based on the cohort of TRD patients, two nested case-control sets were created using incidence density sampling, one in which the outcome was completed suicide and one in which the outcome was suicide attempt. The reason for using a nested case-control design instead of following the full cohort of TRD patients was that we were interested in analyzing the effect of time-varying covariates that were more efficient to measure based on the event time of cases and corresponding time for controls than if the cohort was followed from baseline.

Cases of suicide among patients with TRD were identified through the Swedish Cause of Death Register, which contains information on deaths in Sweden gathered from official death certificates listed as main and contributory causes of death coded according to the current ICD version (Brooke et al., 2017). Following Swedish suicide research guidelines (National Centre for Suicide Research and Prevention of Mental Ill-Health, 2019), a suicide case was defined as presence of the ICD-10 codes X60–X84 (intentional self-harm) or Y10–Y34 (event of undetermined intent, the majority of which are misclassified suicides; Lachaud et al., 2017) as cause of death. Cases with suicide attempts among patients with TRD were identified using the ICD-10 codes X60–X84 and Y10–Y34 in the NPR.

For each case of suicide or suicide attempt, three controls who were alive at the time of the case and had not yet experienced the event of interest (suicide and suicide attempt, respectively) were selected using incidence density sampling among all patients currently fulfilling TRD criteria. The case-control ratio was determined through weighing statistical power against the number of controls available for each case. Cases and controls were matched on age at entry into the MDD cohort (in the categories of 18–29, 30–39, 40–49, 50–59, and 60–69 years of age), sex, time between entry into MDD cohort and fulfillment of TRD criteria in six categories (equal $N$ in each category, percentile distribution), and time since fulfillment of TRD criteria (the time scale used for the incidence density sampling).

## Exposures

The following sociodemographic outcomes were selected for study from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), which is held by the government agency Statistics Sweden: (1) annual income level in relation to the income distribution in Sweden, stratified as lower 20% bracket, middle income, or top 20%; (2) birth country, grouped as Sweden, Europe, or other; (3) education level, stratified as missing, ≤9 years, 10 to 12 years, or ≥13 years; (4) and being married (yes/no). Income level, educational level, and marital status were assessed in the calendar year prior to MDD cohort inclusion.

Furthermore, data on the following clinical outcomes were selected from the NPR, using data from 2001 onward and measured up to the matching date: (5) previous self-harm/suicide attempt (ICD-10: X60–X84 or Y10–Y34), hierarchically stratified as ≤1 year before time of the suicide or suicide attempt, >1 year, and no occurrence; (6) history of substance use

disorders, defined as occurrence of substance use disorders in the NPR (ICD-10: F10–F16 or F18–F19) and/or drugs for treatment of substance use disorders (disulfiram, acamprosate, naltrexone, nalmefene, or methadone or buprenorphine for opioid abstinence) in the PDR; (7) comorbid anxiety disorders (ICD-10: F40–F41); (8) comorbid personality disorders (ICD-10: F60–F61); (9) a history of at least one previous depressive episode (ICD-10: F32–F33) before the first antidepressant prescription in this study, hierarchically stratified by ≤1 year and >1 year, and (10) somatic comorbidity, expressed as Charlson Comorbidity Score (27) constructed from diagnostic data in the NPR from 2001 onward, in the strata of 0, 1 to 2 and 3+ major comorbidities.

## Statistical Analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) comparing cases with controls regarding the exposures were calculated for both suicide and suicide attempts, first in univariable and then in multivariable conditional logistic regression models including all exposures. If several suicide attempts were registered, only the first was used for matching and comparison of cases and controls. Since analyses were performed separately for the two outcomes, a case or control could be included in both. In addition, stratified analyses were also performed on the matching variable of sex and on age in strata of ≤29, 30 to 49, and ≥50 to 69 years at the first antidepressant prescription. Furthermore, due to the strong statistical influence of history of suicide attempts in the model with suicide as outcome, a post hoc sensitivity analysis was performed including only the 93 suicide cases without any history of suicide

attempts. A post hoc analysis stratified on personality disorders was also performed. In these models, matching was broken due to uneven distribution between cases and controls, and the analysis instead adjusted for the matching variables.

## ETHICAL APPROVAL

The study was approved by the regional ethical review board in Stockholm (no. 2017/1236-31/2).

## RESULTS

During the time period of 2006 to 2014, a total of 15,631 (12.8%) patients in the MDD cohort fulfilled criteria for TRD. Of these 8,645 (58%) were women. During the study period, there were 178 (1.1%) deaths from suicide during 54,698 person-years and 1,242 (7.9%) registered suicide attempts during 50,893 person-years among patients with TRD.

Descriptive data on cases of suicide and suicide attempts are displayed in Table 1. A majority of suicide cases were men (61%). Suicide was slightly more common in the age strata of 18 to 29 years (24% of cases) and 60 to 69 years (22%). In contrast, among patients with suicide attempts a majority of cases were women (62%), with the highest proportion of patients in the youngest age stratum, 18 to 29 years (48%), and thereafter decreasing. Frequencies of the specific anxiety and personality disorder diagnoses among cases and controls are displayed in Supplemental Table 1.

TABLE 1.  Characteristics of Cases and Controls With Treatment-Resistant Depression

|  | Suicide cases (%) | Controls (%) | Suicide attempt cases (%) | Controls (%) |
|---|---|---|---|---|
| Total | 178 (100) | 534 (100) | 1,242 (100) | 3,726 (100) |
| Sex |  |  |  |  |
| Male | 109 (61) | 327 (61) | 469 (38) | 1,407 (38) |
| Female | 69 (39) | 207 (39) | 773 (62) | 2,319 (62) |
| Age group |  |  |  |  |
| 18–29 | 42 (24) | 126 (24) | 598 (48) | 1,794 (48) |
| 30–39 | 32 (18) | 96 (18) | 254 (20) | 762 (20) |
| 40–49 | 32 (18) | 96 (18) | 192 (15) | 576 (15) |
| 50–59 | 33 (18) | 99 (18) | 131 (11) | 393 (11) |
| 60–69 | 39 (22) | 117 (22) | 67 (5) | 201 (5) |

## Risk Factors for Suicide

Results from univariable and multivariable analyses of risk factors for suicide are displayed in Table 2. In the *univariable* analyses, a suicide attempt was associated with suicide, both within 1 year (OR, 8.91; 95% CI, 5.05–15.7) and after more than 1 year (OR, 4.45; 95% CI, 2.52–7.86). Furthermore, substance use disorders (OR, 2.92; 95% CI, 2.01–4.25), anxiety disorders (OR, 1.55; 95% CI, 1.09–2.1), and personality disorders (OR, 2.20; 95% CI, 1.34–3.62) were associated with suicide. A Charlson Comorbidity Index of 1 to 2 showed borderline significance for association with suicide compared to no comorbidity (OR, 1.53; 95% CI, 1.00–2.36), but higher comorbidity did not affect the suicide risk. We found no statistically significant associations in the univariable analyses between suicide and income, education level, marital status, birth country, or previous MDD episodes.

In the *multivariable* analysis, the strongest association, with an eightfold risk increase, was found for a history of suicide attempt within the last year (adjusted odds ratio [aOR], 8.76; 95% CI, 4.54–16.9), while suicide attempts more than a year ago increased the risk nearly fourfold (aOR, 3.57; 95% CI, 1.91–6.70). The higher levels of attained education of 10 to 12 and >12 years emerged as significant and borderline significant risk factors (10–12 years aOR, 1.69; 95% CI, 1.02–2.81; <12 years aOR, 1.69; 95% CI, 0.96–2.96).

## Risk Factors for Suicide Attempts

Results from univariable and multivariable analyses of risk factors for suicide attempts are shown in Table 3. In *univariable* analyses, being born outside of Sweden showed a negative association with risk for suicide attempts (Europe aOR, 0.68; 95% CI, 0.54–0.87; rest of the world aOR, 0.60; 95% CI, 0.46–0.77). An attained level of education >12 years (aOR, 0.68; 95% CI, 0.57–0.82) and being married (aOR, 0.76; 95% CI, 0.64–0.90) were negatively associated with suicide attempts. History of suicide attempts was strongly associated with a new attempt, both within one year (aOR, 7.18; 95% CI, 5.70–9.04) and over a year later (aOR, 3.99; 95% CI, 3.24–4.91). Psychiatric comorbidities were associated with risk of suicide attempts: substance use

*TABLE 2.* **Risk Factors for Suicide Among Patients With Treatment-Resistant Depression (TRD)**

| | Cases | Controls[a] | Univariable OR (95% CI) | Multivariable aOR (95% CI)[b] |
|---|---|---|---|---|
| Total | 178 | 534 | | |
| **Income group** | | | | |
| Bottom 20% | 82 (46) | 239 (45) | Ref. | Ref. |
| Middle | 91 (51) | 266 (50) | 0.99 (0.68–1.42) | 0.93 (0.60–1.45) |
| Top 20% | 5 (3) | 29 (5) | 0.50 (0.18–1.35) | 0.47 (0.16–1.36) |
| **Education level** | | | | |
| Missing | 1 (0.6) | 1 (0.2) | – | – |
| Up to 9 years | 40 (22) | 138 (26) | Ref. | Ref. |
| 10–12 years | 85 (48) | 241 (45) | 1.23 (0.80–1.89) | **1.69 (1.02–2.81)** |
| >12 years | 52 (29) | 154 (29) | 1.17 (0.72–1.91) | 1.69 (0.96–2.96) |
| **Married** | | | | |
| No | 125 (70) | 361 (68) | Ref. | Ref. |
| Yes | 53 (30) | 173 (32) | 0.87 (0.59–1.29) | 1.27 (0.71–1.79) |
| **Birth country** | | | | |
| Sweden | 149 (84) | 417 (78) | Ref. | Ref. |
| Europe | 13 (9) | 61 (11) | 0.60 (0.32–1.12) | 0.49 (0.24–1.03) |
| Other | 13 (9) | 56 (10) | 0.81 (0.45–1.44) | 0.58 (0.29–1.18) |
| **History of suicide attempt** | | | | |
| No | 93 (52) | 458 (86) | Ref. | Ref. |
| ≤1 year ago | 51 (29) | 33 (6) | **8.91 (5.05–15.7)** | **8.76 (4.54–16.9)** |
| >1 year ago | 34 (19) | 43 (8) | **4.45 (2.52–7.86)** | **3.57 (1.91–6.70)** |
| **Substance use disorder** | | | | |
| No | 102 (57) | 424 (79) | Ref. | Ref. |
| Yes | 76 (43) | 110 (21) | **2.92 (2.01–4.25)** | 1.40 (0.85–2.29) |
| **Anxiety disorder** | | | | |
| No | 83 (47) | 303 (57) | Ref. | Ref. |
| Yes | 95 (53) | 231 (43) | **1.55 (1.09–2.22)** | 1.27 (0.84–1.92) |
| **Personality disorder** | | | | |
| No | 146 (82) | 484 (91) | Ref. | Ref. |
| Yes | 32 (18) | 50 (9) | **2.20 (1.34–3.62)** | 1.22 (0.68–2.20) |
| **History of depression** | | | | |
| No | 115 (65) | 362 (68) | Ref. | Ref. |
| ≤1 year ago | 43 (24) | 117 (22) | 1.17 (0.76–1.79) | 0.90 (0.54–1.48) |
| >1 year ago | 20 (11) | 55 (10) | 1.13 (0.66–1.96) | 0.99 (0.53–1.87) |
| **Charlson's comorbidity index** | | | | |
| 0 | 129 (72) | 423 (79) | Ref. | Ref. |
| 1–2 | 44 (25) | 99 (19) | 1.53 (1.00–2.36) | 1.31 (0.80–2.15) |
| ≥3 | 5 (3) | 12 (2) | 1.51 (0.52–4.37) | 1.07 (0.31–3.65) |

[a]Matched on sex, age, time between having both a major depressive disorder diagnosis and an index antidepressant prescription and time for fulfillment of TRD definition, as well as time since fulfillment of TRD definition.
[b]Adjusted for all covariates.
Results from univariable and multivariable conditional logistic regression analyses expressed as odds ratios (ORs) and adjusted OR (aORs) with 95% confidence intervals (CIs).

*TABLE 3.* **Risk Factors for Suicide Attempt Among Patients With Treatment-Resistant Depression**

| | Cases | Controls[a] | Univariable OR (95% CI) | Multivariable aOR (95% CI)[b] |
|---|---|---|---|---|
| Total | 1,242 | 3,726 | | |
| Income group | | | | |
|   Bottom 20% | 704 (57) | 2,016 (54) | Ref. | Ref. |
|   Middle | 524 (42) | 1,644 (44) | 0.91 (0.79–1.04) | 1.02 (0.87–1.19) |
|   Top 20% | 14 (1) | 66 (2) | 0.60 (0.34–1.08) | 0.72 (0.37–1.41) |
| Birth country | | | | |
|   Sweden | 1,070 (86) | 2,995 (80) | Ref. | Ref. |
|   Europe | 91 (7) | 362 (10) | **0.68 (0.54–0.87)** | 0.76 (0.58–1.01) |
|   Other | 81 (7) | 369 (10) | **0.60 (0.46–0.77)** | **0.68 (0.50–0.90)** |
| Education level | | | | |
|   Missing | 6 (0.5) | 31 (1) | – | – |
|   Up to 9 years | 360 (29) | 922 (25) | Ref. | Ref. |
|   10–12 years | 609 (49) | 1,779 (48) | 0.88 (0.75–1.02) | 0.95 (0.80–1.14) |
|   >12 years | 267 (22) | 994 (27) | **0.68 (0.57–0.82)** | 0.84 (0.67–1.04) |
| Married | | | | |
|   No | 986 (79) | 2,803 (75) | Ref. | Ref. |
|   Yes | 256 (21) | 923 (25) | **0.76 (0.64–0.90)** | 0.97 (0.80–1.18) |
| History of suicide attempt | | | | |
|   No | 755 (61) | 3,303 (89) | Ref. | Ref. |
|   ≤1 year ago | 262 (21) | 174 (5) | **7.18 (5.70–9.04)** | **5.10 (3.98–6.52)** |
|   >1 year ago | 225 (18) | 249 (7) | **3.99 (3.24–4.91)** | **2.50 (1.98–3.15)** |
| Substance use disorder | | | | |
|   No | 664 (53) | 3051 (82) | Ref. | Ref. |
|   Yes | 578 (47) | 675 (18) | **4.00 (3.45–4.62)** | **2.59 (2.20–3.06)** |
| Anxiety disorder | | | | |
|   No | 499 (40) | 2,003 (54) | Ref. | Ref. |
|   Yes | 743 (60) | 1,723 (46) | **1.74 (1.52–1.98)** | **1.27 (1.09–1.48)** |
| Personality disorder | | | | |
|   No | 935 (75) | 3,329 (89) | Ref. | Ref. |
|   Yes | 307 (25) | 397 (11) | **2.98 (2.50–3.55)** | **1.87 (1.52–2.29)** |
| History of depression | | | | |
|   No | 722 (58) | 2617 (70) | Ref. | Ref. |
|   ≤1 year ago | 347 (28) | 798 (21) | **1.65 (1.41–1.93)** | **1.21 (1.01–1.46)** |
|   >1 year ago | 173 (14) | 311 (8) | **2.05 (1.67–2.51)** | **1.35 (1.06–1.71)** |
| Charlson's comorbidity index | | | | |
|   0 | 948 (76) | 3134 (84) | Ref. | Ref. |
|   1–2 | 270 (22) | 564 (15) | **1.63 (1.38–1.93)** | **1.40 (1.15–1.69)** |
|   ≥3 | 24 (2) | 28 (1) | **3.25 (1.83–5.78)** | **2.00 (1.03–3.88)** |

[a]Matched on sex, age, time between having both a major depressive disorder diagnosis and an index antidepressant prescription and time for fulfillment of TRD definition, as well as time since fulfillment of TRD definition.
[b]Adjusted for all covariates.
Results from univariable and multivariable conditional logistic regression analyses expressed as odds ratios (ORs) and adjusted OR (aORs) with 95% confidence intervals (CIs).

disorders (aOR, 4.00; 95% CI, 3.45–4.62), anxiety (aOR, 1.74; 95% CI, 1.52–1.98), and personality disorders (aOR, 2.98; 95% CI, 2.50–3.55). Also associated with risk of suicide attempts were recurrent depressive episodes, both if within 1 year (aOR, 1.65; 95% CI, 1.41–1.93) and if more than a year ago (aOR, 2.05; 95% CI, 1.67–2.51). Finally, a larger burden of somatic comorbidity was associated with suicide attempts (Charlson's comorbidity index 1–2: aOR, 1.63; 95% CI, 1.38–1.93; Charlson's comorbidity index ≥3: aOR, 3.25; 95% CI, 1.83–5.78). There was no significant association with income level.

In the *multivariable* analysis, all psychiatric and somatic comorbidities retained their significant association with risk of suicide attempts, albeit with in general lower point estimates and wider CIs. The strongest independent risk factors were suicide attempt within 1 year with a fivefold risk increase (aOR, 5.10; 95% CI, 3.98–6.52) and substance use disorders (aOR, 2.59; 95% CI, 2.20–3.06).

## Stratified Analyses

Results were similar for both suicide and suicide attempts in analyses stratified by sex, age (Supplemental Tables 2–5), and personality disorders (not shown), although with wider CIs due to less power. In the post hoc analysis including only the 93 suicide cases without any history of suicide attempts, results were similar but again with wider CIs (Supplemental Table 8). In this analysis, substance use disorders emerged as an independent risk factor for suicide in the multivariable analysis (aOR, 1.92; 95% CI, 1.07–3.42).

## DISCUSSION

### Main Findings

In this nested case-control study, we found that a history of suicide and higher levels of education were independent risk factors for completed suicide among patients with TRD, while history of suicide attempts and various psychiatric comorbidities were the strongest risk factors for suicide attempts.

### Strengths and Weaknesses

The strengths of this study include the use of Swedish administrative health registers, with nationwide coverage and a very small amount of missing data (Brooke et al., 2017; Ludvigsson et al., 2011, 2016). For investigation of suicide and suicide attempts, register studies in general have advantages compared to clinical studies as patients at risk for suicide will often be excluded from the latter or be subject to preventive measures (Preskorn, Macaluso, & Trivedi, 2015). The nested case-control design with density sampling used in this study also allows for the interpretation of ORs as incidence rate ratios, i.e., relative risks (Rothman, 2012).

Weaknesses of this study include that the definition of TRD used here is a model for use in administrative data and, as such, does not include information regarding severity or type of MDD (e.g., melancholic or psychotic) or underlying reasons for treatment switch, continuation, or discontinuation of treatment. Second, although the clinical validity of the diagnoses in the NPR is generally high, the specific diagnoses of MDD, substance use disorders, personality disorders, and several of the anxiety disorders have as yet not been clinically validated on a larger scale

(Ludvigsson et al., 2011). However, only diagnoses in specialized care were included, which is likely to have increased precision and validity. Third, power in the multivariable analyses for suicide was generally low with wide CIs. Fourth, patients may have received other treatments not covered by the registers, including psychotherapy or lifestyle counseling, both before or after the study period. And fifth, ICD-10 codes do not allow for discrimination of suicide attempts or non-suicidal self-injury (NSSI), which may lead to misclassification. This is especially important considering that 25% of the patients with suicide attempts had been diagnosed with personality disorders, most frequently borderline personality disorder (BPD, 14%; Supplemental Table 1). On the other hand, while NSSI is very common in BPD, so is self-injury with at least partial suicidal intent, as exemplified by the 7% with personality disorders among the suicide cases in this study who had a BPD diagnosis, as well as the high risk for suicide among patients with BPD (Black, Blum, Pfohl, & Hale, 2004). Presence of self-injurious behavior in BPD doubles the patient's risk of suicide (Gunderson & Ridolfi, 2006) and was a strong independent risk factor in the present study. The use of codes that do not discriminate between suicide attempt and NSSI may also to some effect reflect the clinical setting where the extent of actual suicidal intent may be unclear when patients present with self-harm.

## Clinical Risk Factors

Results from this study are generally in line with the published literature regarding patients with MDD. It is well established that a history of suicide attempts, regardless of underlying diagnosis, is the most important risk factor for completed suicide. A systematic review, which pooled seven studies with depressed patients and identified a total of 347 suicide cases, reported that suicide attempts/self-harm were associated with an overall risk increase for suicide of 4.9 (3.4–7.2; Hawton, Casanas, Haw, & Saunders, 2013). Likewise, the psychiatric comorbidities of substance use disorders, anxiety disorders, and personality disorders are established risk factors for both suicide and suicide attempts (Crump et al., 2014; Dumais et al., 2005). The underlying mechanism of comorbidity may be related to clinical factors such as lessened impulse control or the synergic increase of burden of psychiatric disability (Nock, Hwang, Sampson, & Kessler, 2010; Turecki, 2005). The association may moreover be complex, as all three examined comorbidities may also increase risk of TRD itself (Souery et al., 2007).

Somatic comorbidity is a well-known risk factor for suicide in the general population but was not identified as such in the present study (Crump et al., 2014). This may be related to power issues but also confounding, as clinicians may be less inclined to administer sequential antidepressant treatment trials among patients with somatic burden, or they may be more sensitive to side effects and treatment cessation, meaning that they are not classified with TRD in this study. However, the association between somatic comorbidity and suicide attempts was clear, suggesting a complex relationship among somatic burden, core depressive symptoms, and perhaps seriousness of intention and ultimate completion of suicide.

## Sociodemographic Risk Factors

Markers of poor sociodemographic status, e.g., regarding attained education

level, income, and marital status, are often regarded as established risk factors for suicide (Agerbo, Qin, & Mortensen, 2006; Cairns, Graham, & Bambra, 2017; Turecki & Brent, 2016), although this has mainly been studied in the general population. When first-time psychiatric patients are studied, the opposite association has been shown, i.e., that employment, high income, and higher education and marriage increase the risk of suicide (Agerbo, 2007; Mortensen, Agerbo, Erikson, Qin, & Westergaard-Nielsen, 2000). The results in the present study suggest that mid- or higher level education may be associated with increased suicide risk among patients with TRD, a pattern also seen in other severe psychiatric disorders and that has been suggested to depend on the loss of higher premorbid functioning (Pompili et al., 2013; Reutfors et al., 2009).

Regarding suicide attempts, lower education seems to increase the risk in the general population (Nock et al., 2008) but, corroborating the findings in the present study of patients with TRD, this was not the case in a study of psychiatric patients (Bhatt et al., 2018). In the present study it is worth noting that close to half of the patients with suicide attempt were <29 years old and may not have had time to complete higher education due to age- and TRD-related disability.

Being married decreased risk of suicide attempts in our study; however, this should be viewed in the context of the large proportion of the Swedish population not being married but living in a cohabitant relationship, decreasing the validity of this variable for use in this context (Ohlsson-Wijk, 2011). Immigrants frequently display a lowered suicide risk in the literature compared to the native population, which is often attributed to a "healthy migrant" effect (Spallek et al.,

2015). This is confirmed regarding the outcome of suicide attempts in the present study but not completed suicide; however, this may be related to low power.

## Clinical Implications

The patients with TRD in this study had undergone several treatment trials and had multiple contacts with health care providers, with opportunity for clinical evaluation and suicide risk assessment. The substantial risk increase among patients with recent suicide attempts in this patient group emphasizes the need for close clinical follow-up, and it has been shown that psychiatric follow-up after a suicide attempt may have a antisuicidal protective effect (Bostwick, Pabbati, Geske, & McKean, 2016). Keeping in mind the elevated risk for suicide in TRD compared to other patients with MDD (Reutfors et al., 2018), and the association between psychiatric comorbidities and suicidality, it seems clear that patients with TRD warrant careful assessment regarding signs and history of suicidal behavior, treatment adherence, and psychiatric and somatic comorbidity in order to prevent unwarranted deaths.

## CONCLUSIONS

Suicide attempts, especially if recent, were strong risk factors for completed suicide among patients with TRD in this study. Established risk factors for suicide attempts were confirmed also for patients with TRD. Further research should elucidate the roles of these risk factors in the assessment of the individual patient and confirm the role of antisuicidal preventive measures as well as intensified treatment efforts for patients with TRD.

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## SUPPLEMENTRY METERIAL

Supplemental data for this article can be accessed at [publisher's weblink].

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