Title: Predictors of Treatment Resistance in Schizophrenia: a population-based cohort study

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FINDINGS Of 8624 patients with schizophrenia, 21.1% fulfilled the TRS proxy definition during follow-up (median 9.1 years, IQR: 6.3-11.9). Younger age, living in a less urban area, higher education, previous psychiatric hospitalization, paranoid subtype, comorbid personality disorder, psychotropic drug use, and previous suicide attempt, were all significantly associated with an increased rate of TRS.

INTERPRETATION The current study identifies several candidate predictors which could potentially be included in future prediction models for TRS. Notably, established risk factors for schizophrenia did not predict TRS, suggesting that TRS may be a distinct subtype of schizophrenia, and not merely a more severe form of schizophrenia.

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Introduction

Treatment-resistant schizophrenia (TRS) is clinically defined as non-response to at least two adequate trials of antipsychotic medication, and is estimated to affect approximately 30% of all patients with schizophrenia.\(^1\) and \(^2\)

Clozapine is the only treatment for TRS with a firm evidence base as reflected by official treatment guidelines\(^2\). Compared with the estimated prevalence of TRS of 30%, the prevalence of clozapine prescription varies from 2-3% in parts of the US\(^3\), to nearly 60% in China\(^3\) and \(^4\) with around 10% in most Western European countries including Denmark\(^5\). This is partly a consequence of variations between national treatment guidelines.\(^6\) and \(^7\) Moreover, the low rate of clozapine treatment in Western countries likely indicates under-prescription and undue postponement probably due to concerns about severe adverse events and the inconvenience of mandatory regular blood monitoring.\(^8\) and \(^9\) By contrast, antipsychotic polypharmacy is commonly prescribed in TRS – despite the lack of evidence for its efficacy.\(^8\) and \(^10\) The social and economic costs of untreated TRS are high,\(^11\) and duration of insufficiently treated or untreated psychosis is strongly associated with unfavorable long-term outcomes\(^12\). Therefore, identification of patients at high risk of TRS at the time of diagnosing schizophrenia would be of clinical benefit in minimizing the delay to clozapine treatment in TRS patients. The literature on predictors for TRS is sparse and the definition of TRS is not consistent between studies,\(^13\) and more research is needed to identify patient- and disease-related candidate predictors associated with TRS.

A further motivation to identifying candidate predictors for TRS is to elucidate the etiology of TRS. A critical question is whether TRS constitutes the severe end of a spectrum of schizophrenia, or whether TRS represents a distinct neurobiological entity that may respond to fundamentally different treatments in comparison with treatment-responsive schizophrenia. In the former case, the established risk factors for schizophrenia\(^14\)-\(^17\) would be expected to apply even more strongly in TRS,\(^18\) whereas in the latter case, TRS would be expected to have a different profile of risk factors than schizophrenia per se.

Our primary aim of this study was therefore to identify candidate predictors of a treatment-based proxy of TRS – including clozapine treatment and additionally another proxy for non-response to first-line treatment. To elucidate the underlying nature of TRS, our secondary aim was to investigate whether established risk factors for schizophrenia also predict treatment resistance.
Research in context

Evidence before this study
We searched PubMed for English-language publications from the date of inception to September 15, 2015 using the terms “treatment resistant schizophrenia”, “treatment refractory schizophrenia”, “schizophrenia”, “clozapine”, “predictors”, and “risk factors”. Several studies were identified on risk factors for schizophrenia and clozapine treatment, while papers on predictors for treatment-resistant schizophrenia were few and differed in terms of both predictors and outcome definition.

Added value of this study
The current study supports and extends the knowledge on predictors for treatment-resistant schizophrenia by identifying several candidate predictors associated with treatment-resistant schizophrenia in a large population-based cohort. These candidate predictors obtained at baseline were: younger age at diagnosis, living in less urban areas, paranoid schizophrenia subtype, a history of psychiatric hospitalization, personality disorder, suicide attempts, and psychotropic drug use. Three different treatment-based proxy measures for treatment-resistant schizophrenia were examined and showed overall similar results. The most striking finding is that living in the capital area is associated with decreased rate of treatment resistance, despite urban living being a risk factor of schizophrenia in general. This suggests treatment-resistant schizophrenia being an etiological distinct subtype of schizophrenia.

Implications of all the available evidence
The candidate predictors identified in this study could potentially be included in a clinical prediction model predicting who will require clozapine early after diagnosis of schizophrenia. Moreover, the findings might help to elucidate the underlying nature of treatment-resistant schizophrenia; i.e. whether it is only a more severe form of schizophrenia, or whether it also defines a distinct subtype of schizophrenia, as hypothesized in other pertinent research.
Methods

Data sources
The unique personal identification number assigned to all persons living in Denmark was used to link individual data across the national registration systems. We obtained information on sex, date of birth, and parents' personal identification numbers from the Danish Civil Registration System established in 1968.19 We obtained information on admission dates and diagnoses (WHO International Classification of Diseases (ICD) version 8 and 10, see supplementary table A1) both from the Danish Psychiatric Central Research Register, and from the Danish National Patient Registry, containing information from all Danish hospitals.20 and 21 The Danish National Prescription Registry provided individual-level pharmacy-based information on all drug prescriptions since 1995.22 Socio-demographic information such as employment status, highest completed education level and marital status was obtained from the Danish Integrated Database for Labour Market and education registries via Statistics Denmark.23 We identified previous convictions for violent offences from the Central Criminal Register established in 1979.24 Complete information from all registries was available until December 31, 2010.

Study cohort
We performed a population-based cohort study, where the study cohort consisted of all patients born in Denmark after 1955, with a first recorded schizophrenia diagnosis (ICD-8 code 295.x9, excl. 295.79; ICD-10 code F20) at age 18 or older between January 1, 1996 and December 31, 2006. Patients were followed from the date of the first schizophrenia diagnosis until emigration, death, or December 31, 2010, whichever came first. Date of first diagnosis (baseline) was defined as the first contact (admission date if inpatient) leading to a schizophrenia diagnosis. We excluded patients dying during first admission and those redeeming clozapine prior to the first schizophrenia diagnosis (see figure 1).25

Assessment of Treatment-Resistant Schizophrenia
Our main TRS proxy was based only on patients’ antipsychotic prescription redemptions and psychiatric hospitalizations, and reflected previous and current Danish and international treatment guidelines2 and 26-30, and was defined as the earliest instance of either (i) first clozapine prescription redemption or (ii) meeting the eligibility criteria for clozapine, here defined as psychiatric hospital admission due to schizophrenia during antipsychotic treatment (as a proxy for insufficient treatment response) within 18 months after having had two periods of different antipsychotic monotherapy of at least six weeks duration. To account for antipsychotic treatment periods prior to first schizophrenia diagnosis we included prescription
redemptions during the year prior to the first schizophrenia diagnosis. In addition, we defined two alternative TRS proxy definitions, cf. figure 2. For further details see supplementary table A2.

**Figure 2 approximately here**

**Assessment of candidate predictors of TRS**
We selected candidate predictors based on a literature search on risk factors for TRS or schizophrenia. We included identified factors which were available in the registers at first schizophrenia diagnosis. We defined two categories of candidate predictors available at baseline, i.e. at first schizophrenia diagnosis: patient-related and disease-related factors.

**Patient-related factors**
We included the following baseline factors (dichotomous variables unless otherwise specified, cf. table 1): female sex, age (continuous), family history of schizophrenia (first-degree relatives), season of birth (born December-March), paternal age (continuous), early parental loss (before age 18), living alone, previous conviction for violent offence, primary (lowest) education level, employment status (4 levels), and urbanicity at first schizophrenia diagnosis (3 levels).

**Disease-related factors**
In addition we included the following baseline factors (dichotomous variables unless otherwise specified, cf. table 1): number of bed days at psychiatric hospital in year prior to first schizophrenia diagnosis (3 levels), admission at psychiatric hospital, paranoid subtype, prior comorbid psychiatric diagnoses (table 1, defined by ICD-8 and ICD-10 codes cf. supplementary table A1), and psychotropic drugs redeemed in year prior to schizophrenia diagnosis; antipsychotics (ATC-code N05A, except N05AN01), antidepressants (ATC-code N06A), and benzodiazepines (ATC code N03AE, N05BA, N05CD, and N05CF).

**Statistical methods**
We performed multivariable Cox proportional hazards regression of the time to TRS to estimate the association between baseline candidate predictors and TRS. We chose Cox proportional hazards regression instead of a multivariable logistic regression model for prediction to account for varying time to TRS and to allow for censoring. We included a total of 23 candidate predictors in the model. Bipolar disorder, autism and attention deficit hyperactivity disorder were excluded due to low prevalence (table 1). The proportional hazards assumption was assessed in diagnostic plots (not shown, available upon request). All statistical analyses were conducted in Stata 13 (StataCorp LP, College Station, TX, USA). All statistical tests were two-sided and deemed significant at a level of 5%. All hazard ratio (HR)
estimates are accompanied by 95% confidence intervals. For evaluation of the model we report
McFadden estimated pseudo $R^2$ for explained variability, and Harrell's C statistic as a measure for how
well the model discriminated TRS from non-TRS.

**Sensitivity analyses**

The robustness of the results with respect to the outcome definition was explored by use of 1) a narrow
TRS definition only including patients initiating clozapine, and 2) a broader TRS definition comprising
patients who fulfilled the main TRS definition and additionally patients who were prescribed
antipsychotic polypharmacy continuously for at least 90 days – a common management to treatment
resistance in clinical practice in Denmark and internationally (figure 2). We repeated the main analysis
censoring the data after two years follow-up to predict TRS occurring within the first two years only, to
mimic current definitions of TRS and to limit the potential violations of the proportional hazards
assumption due to long-term follow-up. We also repeated the main analysis restricted to new users of
antipsychotics to evaluate the influence of prior antipsychotic use. Furthermore, we estimated HRs for
each candidate predictor independently in models only including sex, age and year of diagnosis, to
estimate independent associations with TRS and to check robustness of results. In addition, we conducted
a Cox regression analysis where the baseline hazard was stratified on sex, age group (see table 1), and
education level (primary versus higher). To evaluate the sensitivity due to missing values, we conducted
analyses where missing values were replaced by the most extreme values (high vs. low).

**Results**

**Participants**

We included 8624 schizophrenia patients fulfilling the inclusion criteria (figure 1). Of those, 7749
(89.9%) were followed until the end of the study period, 763 (8.9%) died and 115 (1.3%) emigrated
during follow-up. The total number of person-years was 77 888 with median follow-up of 9.1 years (IQR:
6.3-11.9 years).

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**Baseline characteristics across groups meeting different criteria indicating TRS**

Of the study population 1137 (13.2%) redeemed at least one clozapine prescription (i), 990 (11.5%) were
hospitalized after two periods of different antipsychotic monotherapy (ii), and 3773 (43.8%) are
treated with polypharmacy for at least 90 days (iii). Overall, patients meeting criteria (i), (ii), or (iii)
indicating TRS during follow-up had a different distribution of baseline characteristics from those not
meeting any of the three criteria indicating TRS, e.g. they were more likely to be female and younger at first schizophrenia diagnosis, living in less urban areas, having a history of psychiatric hospitalization, comorbid psychiatric diagnoses, and psychotropic medication. In particular, patients meeting criteria (i) and (ii) were very similar regarding most baseline characteristics (table 1).

**Candidate predictors of TRS**

In multivariable complete case analyses 1703 (21.2%) out of the total of 8044 fulfilled the main TRS proxy definition (criteria (i) or (ii), whichever came first). Baseline factors significantly associated with increased TRS were: younger age, living in less urban areas, higher education, psychiatric hospital admission at first schizophrenia diagnosis, having spent more than 30 bed days at psychiatric hospital in the previous year, paranoid subtype, comorbid personality disorder, suicide attempt, and psychotropic drug use (antipsychotics, antidepressants and benzodiazepines) (table 2).

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Crude cumulative incidences of TRS are plotted stratified on sex, age at first schizophrenia diagnosis, hospital days in the previous year, and levels of urbanicity (figure 3).

The variance explained by the full model was 2.7% (McFadden estimated pseudo $R^2$) while the C-statistic was 0.70 indicating that the model discriminated sufficiently between TRS and non-TRS-patients. Both statistics though do not take censoring into account.

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**Sensitivity analyses**

In table 2, we showed - in addition to the results of the main TRS proxy – the results of similar analyses using 1) the more narrow TRS proxy of clozapine initiation only, and 2) the broader TRS proxy including 90-day polypharmacy. The alternative definitions resulted in similar estimates in terms of the size and direction of estimates (table 2). Moreover, long-term disability benefit, no substance abuse, and diagnosis of schizoaffective disorder, were marginally significantly associated with increased risk of subsequently taking clozapine. The broader TRS proxy including polypharmacy was associated with early parental loss, low education, long-term disability benefit, depression and substance abuse (table 2). Censoring follow-up to two years gave similar results, and further increased estimates for living in non-urban areas, psychiatric admissions, and psychotropic drug use, and higher education became insignificant (supplementary table A3). Restricting to new users of antipsychotics, the following factors remained significant: younger age, living in less urban areas, psychiatric hospitalization, paranoid subtype,
comorbid personality disorder, and suicide attempt. In addition, female sex was marginally significant (data not shown, available upon request). In models only including sex, age, and calendar year at first schizophrenia diagnosis and additional factors entered individually, education was not associated with TRS, and the following factors – in addition to those identified in the multivariable model – were significantly associated with increased TRS: female sex, previous conviction for violent offence, long-term disability benefit, and prior psychiatric diagnoses listed (supplementary table A4). The analysis where the baseline hazard was stratified on sex, age group, and education level, resulted in similar/identical estimates as those shown in table 2.

**Effect of missingness**

Due to the low rates of missingness (family history (4.1%), paternal age (2.7%), education (2.7%), work status (0.1%)), we performed complete case analysis including 8044 (93.2%) of the 8624 patients in our original study population. Effect estimates resulting from analysis based on the original study population were largely unaffected by extreme value imputation of missing values and none changed direction.

**Discussion**

In this study we identified the following candidate predictors available at first schizophrenia diagnosis, which were significantly associated with increased rates of TRS: younger age, living in less urban areas, higher education, admitted at psychiatric hospital, paranoid subtype, and history of personality disorders, suicide attempts, and previous prescription of psychotropic drugs.

Younger age at first schizophrenia diagnosis was consistently, regardless of TRS definition or model used, associated with increased rate of TRS in accordance with other research.\(^3,5,7,33\)

Disease-related factors such as more bed days in psychiatric hospital in the year prior to first schizophrenia diagnosis as well as hospital admission at first contact leading to a schizophrenia diagnosis were associated with increased TRS indicating that greater illness severity at schizophrenia onset is associated with a more complicated illness course. Prior diagnoses of personality disorder, suicide attempts, and paranoid schizophrenia subtype were all associated with increased TRS, which corroborates previous research.\(^33\)

Male sex, a well-established risk factor for schizophrenia in the general population,\(^17\) was not associated with increased TRS, with a (non-significant) opposite association. Moreover, urbanicity was found to be significantly associated with TRS – interestingly in opposite direction than for schizophrenia incidence in the general population.\(^34\) This finding of increased TRS in less urban areas may partly be explained by
different treatment practices across regions; supported by different rates of clozapine prescribing due to region or type of hospital. However, these findings are consistent with the possibility that, rather than representing a severe form of schizophrenia, the treatment-resistant subtype (i.e. TRS) may have a fundamentally different aetiology than the treatment-responsive subtype of schizophrenia. This fits with the emerging view that TRS may be a non-dopaminergic subtype of schizophrenia, and that TRS patients do not show the increased dopamine synthesis capacity seen in patients responsive to first-line antipsychotics. One possibility is that urban environments may confer increased risk for a ‘dopaminergic’ form of psychosis, mediated by dopamine synthesis, which is responsive to treatment with dopamine-blocking drugs, while the treatment-resistant subtype shows no associations with urbanicity.

Strengths and limitations
A major strength of this study is its size and comprehensiveness - it is a population-based longitudinal cohort study with up to 15 years follow-up of all adult and incident schizophrenia patients in Denmark, with very little missing data. The majority of previous studies on clozapine use or TRS has been cross-sectional or was not analyzed longitudinally. We focused on adult onset schizophrenia, due to differing treatment guidelines and thus different definition of TRS for children. Factors related to clozapine treatment in patients with early onset of schizophrenia in Denmark have been investigated recently.

Several limitations are implicated by the register-based design. Regarding inclusion of candidate predictors or effect modifiers, several factors, such as smoking, body mass index, birth complications such as infection, and duration of untreated psychosis, were not available in the registers or were not suitable for this design only including factors obtainable at first diagnosis of schizophrenia. Regarding the TRS proxy definition we based it on clinical guidelines using data on prescriptions and psychiatric admissions obtainable from the registers. Ideally the definition would have included clinical scores as in the definition of Kane et al., including scores for positive and negative symptoms. However, these scores were not available in the registers. Almost all previous studies have, used proxy measures of TRS. In case of register-based studies, clozapine initiation has largely been used as a proxy. This is, however, not optimal since clozapine is under-prescribed and hence this will not capture all patients with TRS for whom clozapine could be a valid treatment option.

To minimize this limitation we considered not only clozapine treatment (i) as a proxy for treatment resistance, but also considered a treatment-based proxy criteria indicating insufficient treatment response to first-line treatment (ii).
We tested the robustness by applying the narrower and the broader TRS definitions and found that the results with regard to candidate predictors were quite robust across the applied definitions, although estimates did not consistently follow a gradient between the narrow category (clozapine only) through main and broad (including 90-day polypharmacy) categories. On the one hand, clozapine initiation might still be the strongest proxy for TRS, as it is prescribed based on clinical judgement. Assuming that clozapine is prescribed exclusively to patients with TRS, clozapine should have 100% precision for TRS. However, this TRS definition is too narrow to capture all patients with TRS due to the suspected underuse of clozapine in Western populations. Our main TRS definition therefore represents a reasonable trade-off between the two extremes (1. Clozapine initiation only – maximizing precision, and 2. TRS including polypharmacy – maximizing sensitivity), and results in 21.1% meeting the TRS criteria, in line with pertinent research and is further supported by the corroboration of some of the previously identified predictors of TRS, such as younger age, hospitalization, and psychiatric comorbidity.

Though this approach closely reflects the treatment guidelines, we acknowledge that this pragmatic approach of considering patients having been through two antipsychotic monotherapy periods or polypharmacy as treatment resistant may include patients with side effects, poor tolerance or compliance as well as a proportion of treatment-resistant patients. Information on prescribed dosage was not available and thus we might overestimate the number of adequate treatment periods of antipsychotic monotherapy. However, the very short trials on a probable low dosage were left out by restricting to monotherapy periods of at least two subsequent prescription redemptions and at least six weeks duration. Furthermore, information on medication during hospitalization was not available, which may potentially underestimate the number of adequate treatment periods of antipsychotic monotherapy and thus bias the TRS proxy definition. In addition, cost-free medication is sometimes given from the psychiatric hospital up to two years after discharge, which is not registered either. However the TRS proxy definition we have used in the current study appears to be the most appropriate approach for identifying TRS given the information available in registry data.

Our results might also be biased since choice of medication does not only reflect the patients’ treatment resistance or severity of disease, but also the psychiatrists’ prescribing practices and/or patients’ and their relatives’ wishes or refusal of specific treatment. In particular switching from one antipsychotic to another during the early era of introduction of a number of atypical antipsychotics in the 1990s may reflect market penetration of the newer drugs rather than treatment resistance with regard to previously used drugs.

Genetic data was not available for this study cohort. The growing interest of identifying genetic liability for schizophrenia and the increasing availability to collect larger genetic samples suggest that future
studies on prediction of TRS should strive to combine genetic data with the identified clinical and environmental predictors of TRS.

**Conclusion**

The current study used a treatment-based proxy for TRS to extend previous knowledge about predictors for TRS, suggesting that future prognostic studies for TRS should include disease-related factors such as history of other psychiatric diagnoses, suicide attempt, hospitalization and medication, as well as patient-related factors such as sex, age, and urbanicity at first schizophrenia diagnosis. We hope that this study will contribute towards the development of a valid prediction models for identifying patients with TRS early after schizophrenia diagnosis, with potential applications in stratified medicine. Moreover, the findings of this study suggest that TRS may not be simply the severe end of a continuum of schizophrenia but may represent a distinct subtype.
Contributors

Christiane Gasse (CG) and James H MacCabe (JHM) obtained funding for the study. CG, Henrik Støvring, Holger J Sørensen, JHM, and Theresa Wimberley (TW) designed the study and wrote the study protocol. TW performed the data management, statistical analyses and wrote the first draft of the manuscript. Henriette T Horsdal performed quality check of the data management. All authors contributed to discussion of the study design and results, revised the manuscript, and have approved the final manuscript.

Declaration of interests

Dr. Støvring reports personal fees from AbbVie, personal fees from UCB, personal fees from Pfizer, personal fees from Astra Zeneca, outside the submitted work. Dr. MacCabe reports grants from European Union, during the conduct of the study. Dr. Gasse reports grants from European Community's Seventh Framework Programme (FP7/2007-2013), during the conduct of the study; grants from LA-SER Analytica, grants from Eli-Lilly, outside the submitted work.

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Figure and Table legends and footnotes

Figure 1: Flow chart illustrating the inclusion and exclusion criteria for the study population, n=8624.

Figure 2: Criteria indicating TRS, and TRS proxy definitions derived from registry data.

a) Antipsychotic treatment periods are defined from prescription data and a more detail description can be found in supplementary table A2.

Table 1: Baseline characteristics for schizophrenia patients meeting different criteria indicating TRS.

Table 2: Hazard rate ratio (HR) and 95% confidence interval (CI) for TRS (main proxy definition, and two alternative proxy definitions) estimated for each candidate predictor in a multivariable model including all listed baseline factors as well as calendar year at first schizophrenia diagnosis, n=8044.

Figure 3: Crude cumulative incidence curves of TRS based on a competing risks regression with death as a competing event. Cumulative incidences are shown in strata of sex, age at first schizophrenia diagnosis, number of hospital days in previous year, and levels of urbanicity.
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Introduction

Treatment-resistant schizophrenia (TRS) is clinically defined as non-response to at least two adequate trials of antipsychotic medication, and is estimated to affect approximately 30% of all patients with schizophrenia.\(^1\)\(^{,}\)\(^{,}\)\(^2\)

Clozapine is the only treatment for TRS with a firm evidence base as reflected by official treatment guidelines.\(^2\) Compared with the estimated prevalence of TRS of 30%, the prevalence of clozapine prescription varies from 2-3% in parts of the US,\(^3\) to nearly 60% in China\(^3\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^4\) with around 10% in most Western European countries including Denmark.\(^5\) This is partly a consequence of variations between national treatment guidelines.\(^6\)\(^{,}\)\(^{,}\)\(^7\) Moreover, the low rate of clozapine treatment in Western countries likely indicates under-prescription and undue postponement probably due to concerns about severe adverse events and the inconvenience of mandatory regular blood monitoring.\(^8\)\(^{,}\)\(^{,}\)\(^{,}\)\(^9\) By contrast, antipsychotic polypharmacy is commonly prescribed in TRS – despite the lack of evidence for its efficacy.\(^8\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\) The social and economic costs of untreated TRS are high,\(^11\) and duration of insufficiently treated or untreated psychosis is strongly associated with unfavorable long-term outcomes.\(^12\) Therefore, identification of patients at high risk of TRS at the time of diagnosing schizophrenia would be of clinical benefit in minimizing the delay to clozapine treatment in TRS patients. The literature on predictors for TRS is sparse and the definition of TRS is not consistent between studies,\(^13\) and more research is needed to identify patient- and disease-related candidate predictors associated with TRS.

A further motivation to identifying candidate predictors for TRS is to elucidate the etiology of TRS. A critical question is whether TRS constitutes the severe end of a spectrum of schizophrenia, or whether TRS represents a distinct neurobiological entity that may respond to fundamentally different treatments in comparison with treatment-responsive schizophrenia. In the former case, the established risk factors for schizophrenia\(^14\)\(^{-}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\)\(^{,}\) would be expected to apply even more strongly in TRS,\(^18\) whereas in the latter case, TRS would be expected to have a different profile of risk factors than schizophrenia per se.\(^4\)

Our primary aim of this study was therefore to identify candidate predictors of a treatment-based proxy of TRS – including clozapine treatment and additionally another proxy for non-response to first-line treatment. To elucidate the underlying nature of TRS, our secondary aim was to investigate whether established risk factors for schizophrenia also predict treatment resistance.
Research in context

Evidence before this study
We searched PubMed, without date restrictions, for English-language publications from the date of inception to September 15, 2015 using the terms “treatment resistant schizophrenia”, “treatment refractory schizophrenia”, “schizophrenia”, “clozapine”, “predictors”, and “risk factors”. Several studies were identified on risk factors for schizophrenia and clozapine treatment, while papers on predictors for treatment-resistant schizophrenia were few and differed in terms of both predictors and outcome definition.

Added value of this study
The current study supports and extends the knowledge on predictors for treatment-resistant schizophrenia by identifying several candidate predictors associated with treatment-resistant schizophrenia in a large population-based cohort. These candidate predictors obtained at baseline were: younger age at diagnosis, living in less urban areas, paranoid schizophrenia subtype, a history of psychiatric hospitalization, personality disorder, suicide attempts, and psychotropic drug use. Three different treatment-based proxy measures for treatment-resistant schizophrenia were examined and showed overall similar results. The most striking finding is that living in the capital area is associated with decreased rate of treatment resistance, despite urban living being a risk factor of schizophrenia in general. This suggests treatment-resistant schizophrenia being an etiological distinct subtype of schizophrenia.

Implications of all the available evidence
The candidate predictors identified in this study could potentially be included in a clinical prediction model predicting who will require clozapine early after diagnosis of schizophrenia. Moreover, the findings might help to elucidate the underlying nature of treatment-resistant schizophrenia; i.e. whether it is only a more severe form of schizophrenia, or whether it also defines a distinct subtype of schizophrenia, as hypothesized in other pertinent research.
Methods

Data sources
The unique personal identification number assigned to all persons living in Denmark was used to link individual data across the national registration systems. We obtained information on sex, date of birth, and parents' personal identification numbers from the Danish Civil Registration System established in 1968\(,^{19}\) We obtained information on admission dates and diagnoses (WHO International Classification of Diseases (ICD) version 8 and 10, see supplementary Table A1) both from the Danish Psychiatric Central Research Register\(,^{20}\) and from the Danish National Patient Registry, containing information from all Danish hospitals\(,^{20,21}\) The Danish National Prescription Registry provided individual-level pharmacy-based information on all drug prescriptions since 1995\(,^{22}\) Socio-demographic information such as employment status, highest completed education level and marital status was obtained from the Danish Integrated Database for Labour Market and education registries via Statistics Denmark\(,^{23}\) We identified previous convictions for violent offences from the Central Criminal Register established in 1979\(,^{24}\) Complete information from all registries was available until December 31, 2010.

Study cohort
We performed a population-based cohort study, where the study cohort consisted of all patients born in Denmark after 1955, with a first recorded schizophrenia diagnosis (ICD-8 code 295.x9, excl. 295.79; ICD-10 code F20) at age 18 or older between January 1, 1996 and December 31, 2006. Patients were followed from the date of the first schizophrenia diagnosis until emigration, death, or December 31, 2010, whichever came first. Date of first diagnosis (baseline) was defined as the first contact (admission date if inpatient) leading to a schizophrenia diagnosis. We excluded patients dying during first admission and those redeeming clozapine prior to their first schizophrenia diagnosis (see Figure 1).\(^{25}\)

Assessment of Treatment-Resistant Schizophrenia
Our main TRS proxy was based only on patients’ antipsychotic prescription redemptions and psychiatric hospitalizations, and reflected previous and current Danish and international treatment guidelines\(^{2,26-30}\) and was defined as the earliest instance of either (i) first clozapine prescription redemption or (ii) meeting the eligibility criteria for clozapine, here defined as psychiatric hospital admission due to schizophrenia during antipsychotic treatment (as a proxy for insufficient treatment response) within 18 months after having had two periods of different antipsychotic monotherapy of at least six weeks duration. To account for antipsychotic treatment periods prior to first schizophrenia diagnosis we included prescription...
redemptions during the year prior to the first schizophrenia diagnosis. In addition, we defined two alternative TRS proxy definitions, cf. figure 2. For further details see supplementary table A2.

**Figure 2 approximately here**

**Assessment of candidate predictors of TRS**

We selected candidate predictors based on a literature search on risk factors for TRS or schizophrenia. We included identified factors which were available in the registers at first schizophrenia diagnosis. We defined two categories of candidate predictors available at baseline, i.e. at first schizophrenia diagnosis: patient-related and disease-related factors.

**Patient-related factors**

We included the following baseline factors (dichotomous variables unless otherwise specified, cf. table 1): female sex, age (continuous), family history of schizophrenia (first-degree relatives), season of birth (born December-March), paternal age (continuous), early parental loss (before age 18), living alone, previous conviction for violent offence, primary (lowest) education level, employment status (4 levels), and urbanicity at first schizophrenia diagnosis (3 levels).

**Disease-related factors**

In addition we included the following baseline factors (dichotomous variables unless otherwise specified, cf. table 1): number of bed days at psychiatric hospital in year prior to first schizophrenia diagnosis (3 levels), admission at psychiatric hospital, paranoid subtype, prior comorbid psychiatric diagnoses (table 1, defined by ICD-8 and ICD-10 codes31 cf. supplementary table A1), and psychotropic drugs redeemed in year prior to schizophrenia diagnosis; antipsychotics (ATC-code N05A, except N05AN01), antidepressants (ATC-code N06A), and benzodiazepines (ATC code N03AE, N05BA, N05CD, and N05CF).

**Statistical methods**

We performed multivariable Cox proportional hazards regression of the time to TRS to estimate the association between baseline candidate predictors and TRS. We chose Cox proportional hazards regression instead of a multivariable logistic regression model for prediction to account for varying time to TRS and to allow for censoring. We included a total of 23 candidate predictors in the model. Bipolar disorder, autism and attention deficit hyperactivity disorder were excluded due to low prevalence (table 1). The proportional hazards assumption was assessed in diagnostic plots (not shown, available upon request). All statistical analyses were conducted in Stata 13 (StataCorp LP, College
Station, TX, USA). All statistical tests were two-sided and deemed significant at a level of 5%. All hazard ratio (HR) estimates are accompanied by 95% confidence intervals. For evaluation of the model we report McFadden estimated pseudo R² for explained variability, and Harrell's C statistic as a measure for how well the model discriminated TRS from non-TRS.

**Sensitivity analyses**
The robustness of the results with respect to the outcome definition was explored by use of 1) a narrow TRS definition only including patients initiating clozapine, and 2) a broader TRS definition comprising patients who fulfilled the main TRS definition and additionally patients who were prescribed antipsychotic polypharmacy continuously for at least 90 days – a common management to treatment resistance in clinical practice in Denmark and internationally (figure 2). We repeated the main analysis censoring the data after two years follow-up to predict TRS occurring within the first two years only, to mimic current definitions of TRS and to limit the potential violations of the proportional hazards assumption due to long-term follow-up. We also repeated the main analysis restricted to new users of antipsychotics to evaluate the influence of prior antipsychotic use. Furthermore, we estimated HRs for each candidate predictor independently in models only including sex, age and year of diagnosis, to estimate independent associations with TRS and to check robustness of results. In addition, we conducted a Cox regression analysis where the baseline hazard was stratified on sex, age group (see Table 1), and education level (primary versus higher). To evaluate the sensitivity due to missing values, we conducted analyses where missing values were replaced by the most extreme values (high vs. low).

**Results**

**Participants**
We included 8624 schizophrenia patients fulfilling the inclusion criteria (figure 1). Of those, 7749 (89.9%) were followed until the end of the study period, 763 (8.9%) died and 115 (1.3%) emigrated during follow-up. The total number of person-years was 77 888 with median follow-up of 9.1 years (IQR: 6.3-11.9 years).

| Table 1 approximately here |

**Baseline characteristics across groups meeting different criteria indicating TRS**
Of the study population 1137 (13.2%) redeemed at least one clozapine prescription (i), 990 (11.5%) were hospitalized after two periods of different antipsychotic monotherapy (ii), and 3773 (43.8%) are treated with polypharmacy for at least 90 days (iii). Overall, patients meeting criteria (i), (ii), or (iii)
indicating TRS during follow-up had a different distribution of baseline characteristics from those not meeting any of the three criteria indicating TRS, e.g. they were more likely to be female and younger at first schizophrenia diagnosis, living in less urban areas, having a history of psychiatric hospitalization, comorbid psychiatric diagnoses, and psychotropic medication. In particular, patients meeting criteria (i) and (ii) were very similar regarding most baseline characteristics (table 1).

**Candidate predictors of TRS**

In multivariable complete case analyses 1703 (21.2%) out of the total of 8044 fulfilled the main TRS proxy definition (criteria (i) or (ii), whichever came first). Baseline factors significantly associated with increased TRS were: younger age, living in less urban areas, higher education, psychiatric hospital admission at first schizophrenia diagnosis, having spent more than 30 bed days at psychiatric hospital in the previous year, paranoid subtype, comorbid personality disorder, suicide attempt, and psychotropic drug use (antipsychotics, antidepressants and benzodiazepines) (table 2).

**Table 2 approximately here**

Crude cumulative incidences of TRS are plotted stratified on sex, age at first schizophrenia diagnosis, hospital days in the previous year, and levels of urbanicity (figure 3).

The variance explained by the full model was 2.7% (McFadden estimated pseudo $R^2$) while the C-statistic was 0.70 indicating that the model discriminated sufficiently between TRS and non-TRS-patients. Both statistics though do not take censoring into account.

**Figure 3 approximately here**

**Sensitivity analyses**

In table 2, we showed - in addition to the results of the main TRS proxy – the results of similar analyses using 1) the more narrow TRS proxy of clozapine initiation only, and 2) the broader TRS proxy including 90-day polypharmacy. The alternative definitions resulted in similar estimates in terms of the size and direction of estimates (table 2). Moreover, long-term disability benefit prior to schizophrenia diagnosis, no substance abuse, and prior diagnosis of schizoaffective disorder, were marginally significantly associated with increased risk of subsequently taking clozapine. The broader TRS proxy including polypharmacy was associated with early parental loss, low education, long-term disability benefit, depression and substance abuse (table A3). Censoring follow-up to two years gave similar results, and further increased estimates for living in non-urban areas, psychiatric admissions, and psychotropic drug uses, and higher education became insignificant (supplementary table A3).
Restricting to new users of antipsychotics, the following factors remained significant: younger age, living in less urban areas, psychiatric hospitalization, paranoid subtype, comorbid personality disorder, and suicide attempt. In addition, female sex was marginally significant (data not shown, available upon request). In models only including sex, age, and calendar year at first schizophrenia diagnosis and additional factors entered individually, education was not associated with TRS, and the following factors— in addition to those identified in the multivariable model—were significantly associated with increased TRS: female sex, previous conviction for violent offence, long-term disability benefit, and prior psychiatric diagnoses listed (supplementary table A4). The analysis where the baseline hazard was stratified on sex, age group, and education level, resulted in similar/identical estimates as those shown in table 2.

**Effect of missingness**
Due to the low rates of missingness (family history (4.1%), paternal age (2.7%), education (2.7%), work status (0.1%)), we performed complete case analysis including 8044 (93.2%) of the 8624 patients in our original study population. Effect estimates resulting from analysis based on the original study population were largely unaffected by extreme value imputation of missing values and none changed direction.

**Discussion**
In this study we identified the following candidate predictors available at first schizophrenia diagnosis, which were significantly associated with increased rates of TRS: younger age, living in less urban areas, higher education, admitted at psychiatric hospital, paranoid subtype, and history of personality disorders, suicide attempts, and previous prescription of psychotropic drugs.

Younger age at first schizophrenia diagnosis was consistently, regardless of TRS definition or model used, associated with increased rate of risk for TRS in accordance with other research. Disease-related factors such as more bed days in psychiatric hospital in the year prior to first schizophrenia diagnosis as well as hospital admission at first contact leading to a schizophrenia diagnosis were associated with increased TRS indicating that greater illness severity at schizophrenia onset is associated with a more complicated illness course. Prior diagnoses of personality disorder, suicide attempts, and paranoid schizophrenia subtype were all associated with increased TRS, which corroborates previous research. Male sex, a well-established risk factor for schizophrenia in the general population, was not associated with increased TRS, with a (non-significant) opposite association. Moreover, urbanicity was found to be
significantly associated with TRS – interestingly in opposite direction than for schizophrenia incidence in the general population.\(^3\)\(^4\)\(^5\) This finding of increased TRS in less urban areas may partly be explained by different treatment practices across regions; supported by different rates of clozapine prescribing due to region or type of hospital.\(^5\) However, these findings are consistent with the possibility that, rather than representing a severe form of schizophrenia, the treatment-resistant subtype (i.e. TRS) may have a fundamentally different aetiology than the treatment-responsive subtype of schizophrenia. This fits with the emerging view that TRS may be a non-dopaminergic subtype of schizophrenia, and that TRS patients do not show the increased dopamine synthesis capacity seen in patients responsive to first-line antipsychotics.\(^3\)\(^5\)\(^8\) One possibility is that urban environments may confer increased risk for a ‘dopaminergic’ form of psychosis, mediated by dopamine synthesis, which is responsive to treatment with dopamine-blocking drugs, while the treatment-resistant subtype shows no associations with urbanicity.\(^3\)\(^6\)

**Strengths and limitations**

A major strength of this study is its size and comprehensiveness - it is a population-based longitudinal cohort study with up to 15 years follow-up of all adult and incident schizophrenia patients in Denmark, with very little missing data. The majority of previous studies on clozapine use or TRS has been cross-sectional or was not analyzed longitudinally.\(^3\)\(^5\)\(^7\)\(^8\)\(^13\)\(^18\)\(^33\)\(^38\) We focused on adult onset schizophrenia, due to differing treatment guidelines and thus different definition of TRS for children. Factors related to clozapine treatment in patients with early onset of schizophrenia in Denmark have been investigated recently.\(^37\)

Several limitations are implicated by the register-based design. Regarding inclusion of candidate predictors or effect modifiers, several factors, such as smoking, body mass index, birth complications such as infection, and duration of untreated psychosis, were not available in the registers or were not suitable for this design only including factors obtainable at first diagnosis of schizophrenia. Regarding the TRS proxy definition we based it on clinical guidelines using data on prescriptions and psychiatric admissions obtainable from the registers. Ideally the definition would have included clinical scores as in the definition of Kane et al.\(^26\), including scores for positive and negative symptoms.\(^26\) However, these scores were not available in the registers. Almost all previous studies have, used proxy measures of TRS. In case of register-based studies, clozapine initiation has largely been used as a proxy.\(^3\)\(^5\)\(^8\)\(^13\)\(^18\)\(^33\)\(^38\) This is, however, not optimal since clozapine is under-prescribed and hence this will not capture all patients with TRS for whom clozapine could be a valid treatment option.
To minimize this limitation we considered not only clozapine treatment (i) as a proxy for treatment resistance, but also considered a treatment-based proxy criteria indicating insufficient treatment response to first-line treatment (ii).

We tested the robustness by applying the narrower and the broader TRS definitions and found that the results with regard to candidate predictors were quite robust across the applied definitions, although estimates did not consistently follow a gradient between the narrow category (clozapine only) through main and broad (including 90-day polypharmacy) categories. On the one hand, clozapine initiation might still be the strongest proxy for TRS, as it is prescribed based on clinical judgement. Assuming that clozapine is prescribed exclusively to patients with TRS, clozapine should have 100% precision for TRS. However, this TRS definition is too narrow to capture all patients with TRS due to the suspected underuse of clozapine in Western populations. Our main TRS definition therefore represents a reasonable trade-off between the two extremes (1. Clozapine initiation only – maximizing precision, and 2. TRS including polypharmacy – maximizing sensitivity), and results in 21.1% meeting the TRS criteria, in line with pertinent research1 and is further supported by the corroboration of some of the previously identified predictors of TRS, such as younger age, hospitalization, and psychiatric comorbidity.

Though this approach closely reflects the treatment guidelines, we acknowledge that this pragmatic approach of considering patients having been through two antipsychotic monotherapy periods or polypharmacy as treatment resistant may include patients with side effects, poor tolerance or compliance9 as well as a proportion of treatment-resistant patients. Information on prescribed dosage was not available and thus we might overestimate the number of adequate treatment periods of antipsychotic monotherapy. However, the very short trials on a probable low dosage were left out by restricting to monotherapy periods of at least two subsequent prescription redemptions and at least six weeks duration. Furthermore, information on medication during hospitalization was not available, which may potentially underestimate the number of adequate treatment periods of antipsychotic monotherapy and thus bias the TRS proxy definition. In addition, cost-free medication is sometimes given from the psychiatric hospital up to two years after discharge, which is not registered either. However the TRS proxy definition we have used in the current study appears to be the most appropriate approach for identifying TRS given the information available in registry data.

Our results might also be biased since choice of medication does not only reflect the patients’ treatment resistance or severity of disease, but also the psychiatrists’ prescribing practices and/or patients’ and their relatives’ wishes or refusal of specific treatment. In particular switching from one antipsychotic to another during the early era of introduction of a number of atypical antipsychotics in the 1990s may reflect market penetration of the newer drugs rather than treatment resistance with regard to previously used drugs.
Genetic data was not available for this study cohort. The growing interest of identifying genetic liability for schizophrenia, and the increasing availability to collect larger genetic samples, suggests that future studies on prediction of TRS should strive to combine genetic data with the identified clinical and environmental predictors of TRS.

**Conclusion**

The current study used a treatment-based proxy for TRS to extend previous knowledge about predictors for TRS, suggesting that future prognostic studies for TRS should include disease-related factors such as history of other psychiatric diagnoses, suicide attempt, hospitalization and medication, as well as patient-related factors such as sex, age, and urbanicity at first schizophrenia diagnosis. We hope that this study will contribute towards the development of a valid prediction models for identifying patients with TRS early after schizophrenia diagnosis, with potential applications in stratified medicine. Moreover, the findings of this study suggest that TRS may not be simply the severe end of a continuum of schizophrenia but may represent a distinct subtype.
Contributors

Christiane Gasse (CG) and James H MacCabe (JHM) obtained funding for the study. CG, Henrik Støvring, Holger J Sørensen, JHM, and Theresa Wimberley (TW) designed the study and wrote the study protocol. TW performed the data management, statistical analyses and wrote the first draft of the manuscript. Henriette T Horsdal performed quality check of the data management. All authors contributed to discussion of the study design and results, revised the manuscript, and have approved the final manuscript.

Acknowledgement

We thank Mr. Aske Astrup for contributing to discussions concerning the study design, data management and analyses.

Conflicts of interest

Dr. Støvring reports personal fees from AbbVie, personal fees from UCB, personal fees from Pfizer, personal fees from Astra Zeneca, outside the submitted work. Dr. MacCabe reports grants from European Union, during the conduct of the study. Dr. Gasse reports grants from European Community's Seventh Framework Programme (FP7/2007-2013), during the conduct of the study; grants from LA-SER Analytica, grants from Eli-Lilly, outside the submitted work.

Role of funding source

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Reference List


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Figure and Table legends and footnotes

Figure 1: Flow chart illustrating the inclusion and exclusion criteria for the study population, n=8624.

Figure 2: Criteria indicating TRS, and TRS proxy definitions derived from registry data.

a) Antipsychotic treatment periods are defined from prescription data and a more detail description can be found in supplementary Table A2.

Table 1: Baseline characteristics for schizophrenia patients meeting different criteria indicating TRS.

Table 2: Hazard rate ratio (HR) and 95% confidence interval (CI) for TRS (main proxy definition, and two alternative proxy definitions) estimated for each candidate predictor in a multivariable model including all listed baseline factors as well as calendar year at first schizophrenia diagnosis, n=8044.

Figure 3: Crude cumulative incidence curves of TRS based on a competing risks regression with death as a competing event risk. Cumulative incidences are shown in strata of sex, age at first schizophrenia diagnosis, number of hospital days in previous year, and levels of urbanicity.
### Table 1: Baseline characteristics for schizophrenia patients meeting different criteria indicating TRS.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>(i) Clozapine initiation</th>
<th>(ii) Eligible for clozapine</th>
<th>(iii) 90-day polyparmacy</th>
<th>Others not meeting criteria (i), (ii), or (iii)</th>
<th>All diagnosed with schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total, n (%)</strong></td>
<td>1137 (13.2%)</td>
<td>990 (11.5%)</td>
<td>3773 (43.8%)</td>
<td>4470 (51.8%)</td>
<td>8624 (100%)</td>
</tr>
<tr>
<td><strong>Patient-related factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex vs. male sex</td>
<td>478 (42.0%)</td>
<td>458 (46.3%)</td>
<td>1564 (41.5%)</td>
<td>1537 (34.4%)</td>
<td>3248 (37.7%)</td>
</tr>
<tr>
<td>Age at first SZ diagnosis, median (IQR)</td>
<td>26.4 (22.1-32.4)</td>
<td>27.3 (22.5-34.5)</td>
<td>28.2 (23.1-35.2)</td>
<td>29.7 (23.7-36.5)</td>
<td>28.9 (23.4-35.8)</td>
</tr>
<tr>
<td>Family history of SZ vs. not (N=8269)</td>
<td></td>
<td></td>
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<tr>
<td>Parental age, median (IQR) (N=8388)</td>
<td>29.0 (25.2-33.1)</td>
<td>28.7 (25.1-33.1)</td>
<td>28.7 (25.3-34.4)</td>
<td>29.2 (25.4-33.9)</td>
<td>29.0 (25.2-33.7)</td>
</tr>
<tr>
<td>Employment status (N=8620)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>In work</td>
<td>345 (30.3%)</td>
<td>278 (28.1%)</td>
<td>1043 (27.6%)</td>
<td>1444 (32.3%)</td>
<td>2613 (30.3%)</td>
</tr>
<tr>
<td>Outside working force</td>
<td>561 (49.3%)</td>
<td>495 (50.0%)</td>
<td>1803 (47.8%)</td>
<td>2072 (46.4%)</td>
<td>4054 (47.0%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>84 (7.4%)</td>
<td>68 (7.2%)</td>
<td>318 (8.4%)</td>
<td>311 (7.0%)</td>
<td>655 (7.6%)</td>
</tr>
<tr>
<td>Urbanicity (Place of living at time of first SZ diagnosis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Capital area (capital and suburb to the capital)</td>
<td>308 (27.1%)</td>
<td>254 (25.7%)</td>
<td>1073 (28.4%)</td>
<td>1913 (42.8%)</td>
<td>3103 (36.0%)</td>
</tr>
<tr>
<td>Disease-related factors</td>
<td></td>
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<tr>
<td>Bed days at psychiatric hospitals in year prior to first SZ diagnosis</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 days</td>
<td>574 (50.5%)</td>
<td>495 (50.0%)</td>
<td>2129 (56.4%)</td>
<td>3155 (70.6%)</td>
<td>5499 (63.8%)</td>
</tr>
<tr>
<td>1-30 days</td>
<td>200 (17.6%)</td>
<td>202 (20.4%)</td>
<td>699 (18.5%)</td>
<td>683 (15.3%)</td>
<td>1450 (16.8%)</td>
</tr>
<tr>
<td>&gt;30 days</td>
<td>363 (31.9%)</td>
<td>293 (29.6%)</td>
<td>945 (25.0%)</td>
<td>632 (14.1%)</td>
<td>1675 (19.4%)</td>
</tr>
<tr>
<td>In-patient at first SZ diagnosis</td>
<td>747 (65.7%)</td>
<td>634 (64.0%)</td>
<td>2089 (55.4%)</td>
<td>1788 (40.0%)</td>
<td>4125 (47.8%)</td>
</tr>
<tr>
<td>Paranoid subtype at first SZ diagnosis</td>
<td>644 (56.6%)</td>
<td>559 (56.5%)</td>
<td>206 (54.6%)</td>
<td>2307 (51.6%)</td>
<td>459 (53.2%)</td>
</tr>
<tr>
<td><strong>Prior psychiatric diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ affective disorder</td>
<td>67 (5.9%)</td>
<td>53 (5.4%)</td>
<td>190 (5.0%)</td>
<td>124 (2.8%)</td>
<td>336 (3.9%)</td>
</tr>
<tr>
<td>Other SZ spectrum disorders</td>
<td>547 (48.1%)</td>
<td>488 (49.3%)</td>
<td>1791 (47.5%)</td>
<td>1796 (40.2%)</td>
<td>3771 (43.7%)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>43 (3.8%)</td>
<td>48 (4.8%)</td>
<td>159 (4.2%)</td>
<td>161 (3.6%)</td>
<td>341 (4.0%)</td>
</tr>
<tr>
<td>Depression</td>
<td>259 (22.8%)</td>
<td>258 (26.1%)</td>
<td>859 (22.8%)</td>
<td>666 (14.9%)</td>
<td>1596 (18.5%)</td>
</tr>
<tr>
<td>Autism</td>
<td>19 (1.7%)</td>
<td>12 (1.2%)</td>
<td>52 (1.4%)</td>
<td>51 (1.1%)</td>
<td>107 (1.2%)</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>4 (0.4%)</td>
<td>5 (0.5%)</td>
<td>27 (0.7%)</td>
<td>33 (0.7%)</td>
<td>60 (0.7%)</td>
</tr>
<tr>
<td>Substance abuse (including alcohol, cannabis, and smoking use disorders)</td>
<td>365 (32.1%)</td>
<td>378 (38.2%)</td>
<td>1312 (34.8%)</td>
<td>1221 (27.3%)</td>
<td>2650 (30.7%)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>434 (38.2%)</td>
<td>413 (41.7%)</td>
<td>1355 (35.9%)</td>
<td>1055 (23.6%)</td>
<td>2525 (29.3%)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>304 (26.7%)</td>
<td>301 (30.4%)</td>
<td>981 (26.0%)</td>
<td>675 (15.1%)</td>
<td>1727 (20.0%)</td>
</tr>
<tr>
<td><strong>Drugs redeemed in previous year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>644 (56.6%)</td>
<td>612 (61.8%)</td>
<td>2155 (57.1%)</td>
<td>1555 (34.8%)</td>
<td>3901 (45.2%)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>449 (39.5%)</td>
<td>421 (42.5%)</td>
<td>153 (40.6%)</td>
<td>1196 (26.8%)</td>
<td>2846 (33.0%)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>508 (44.7%)</td>
<td>432 (43.6%)</td>
<td>1648 (43.7%)</td>
<td>1197 (26.8%)</td>
<td>2984 (34.6%)</td>
</tr>
</tbody>
</table>
### Table 1: Hazard rate ratio (HR) and 95% confidence interval (CI) for TRS (main proxy definition, and two alternative proxy definitions) estimated for each candidate predictor in a multivariable model including all listed baseline factors as well as calendar year at first schizophrenia diagnosis, n=8044.

<table>
<thead>
<tr>
<th>Patient-related factors</th>
<th>Clozapine only</th>
<th>TRS main</th>
<th>TRS including polypharmacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>1071</td>
<td>1703</td>
<td>3878</td>
</tr>
<tr>
<td>Total person-time at risk (years)</td>
<td>65 657</td>
<td>61 421</td>
<td>47 395</td>
</tr>
<tr>
<td>Rate per 100 person-years</td>
<td>1·62</td>
<td>2·77</td>
<td>8·19</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex versus male sex</td>
<td>1·00 (0·87-1·14)</td>
<td>1·07 (0·96-1·19)</td>
<td>1·04 (0·97-1·12)</td>
</tr>
<tr>
<td>Age at first SZ diagnosis</td>
<td>0·94 (0·93-0·95)</td>
<td>0·96 (0·95-0·97)</td>
<td>0·98 (0·97-0·98)</td>
</tr>
<tr>
<td>Family history of SZ versus not (n=8269)</td>
<td>0·92 (0·72-1·18)</td>
<td>1·00 (0·83-1·21)</td>
<td>1·03 (0·91-1·17)</td>
</tr>
<tr>
<td>Season of birth (Born Dec-March)</td>
<td>0·96 (0·84-1·09)</td>
<td>1·01 (0·91-1·11)</td>
<td>0·97 (0·90-1·03)</td>
</tr>
<tr>
<td>Paternal age (n=8388)</td>
<td>1·00 (0·99-1·01)</td>
<td>1·00 (0·99-1·01)</td>
<td>1·00 (0·99-1·00)</td>
</tr>
<tr>
<td>Early parental loss</td>
<td>0·88 (0·69-1·12)</td>
<td>0·97 (0·81-1·16)</td>
<td>1·16 (1·03-1·30)</td>
</tr>
<tr>
<td>Living alone versus couple</td>
<td>0·99 (0·88-1·12)</td>
<td>1·00 (0·91-1·11)</td>
<td>1·01 (0·95-1·08)</td>
</tr>
<tr>
<td>Violent offence</td>
<td>1·12 (0·91-1·37)</td>
<td>1·04 (0·89-1·23)</td>
<td>0·92 (0·82-1·02)</td>
</tr>
<tr>
<td>Primary education level versus higher (n=8389)</td>
<td>0·83 (0·72-0·95)</td>
<td>0·88 (0·79-0·98)</td>
<td>1·09 (1·01-1·17)</td>
</tr>
<tr>
<td>Employment status (n=8620)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In work</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Outside working force</td>
<td>0·95 (0·83-1·10)</td>
<td>1·01 (0·90-1·13)</td>
<td>1·06 (0·98-1·14)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>0·86 (0·67-1·09)</td>
<td>0·95 (0·79-1·15)</td>
<td>0·94 (0·83-1·07)</td>
</tr>
<tr>
<td>Long-term disability benefit</td>
<td>1·23 (0·98-1·55)</td>
<td>1·14 (0·95-1·36)</td>
<td>1·32 (1·17-1·47)</td>
</tr>
<tr>
<td>Urbanicity (Place of living at time of first schizophrenia diagnosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital area (capital and suburb to the capital)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Provincial area (&gt;10,000 inhabitants)</td>
<td>1·40 (1·21-1·63)</td>
<td>1·38 (1·23-1·56)</td>
<td>1·38 (1·27-1·49)</td>
</tr>
<tr>
<td>Rural area</td>
<td>1·40 (1·18-1·67)</td>
<td>1·44 (1·25-1·65)</td>
<td>1·61 (1·47-1·76)</td>
</tr>
<tr>
<td>Disease-related factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bed days (psyc) in year prior to first schizophrenia diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 days</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1-30 days</td>
<td>1·07 (0·90-1·28)</td>
<td>1·11 (0·96-1·27)</td>
<td>1·04 (0·95-1·14)</td>
</tr>
<tr>
<td>&gt;30 days</td>
<td>1·62 (1·38-1·91)</td>
<td>1·54 (1·35-1·75)</td>
<td>1·30 (1·19-1·42)</td>
</tr>
<tr>
<td>In-patient at first schizophrenia diagnosis</td>
<td>2·06 (1·81-2·34)</td>
<td>2·07 (1·87-2·29)</td>
<td>1·63 (1·53-1·74)</td>
</tr>
<tr>
<td>Paranoid subtype at first schizophrenia diagnosis</td>
<td>1·31 (1·16-1·48)</td>
<td>1·24 (1·13-1·37)</td>
<td>1·15 (1·08-1·23)</td>
</tr>
<tr>
<td>Prior psychiatric diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ affective disorder</td>
<td>1·28 (0·99-1·65)</td>
<td>1·18 (0·95-1·45)</td>
<td>1·14 (0·98-1·31)</td>
</tr>
<tr>
<td>Other SZ spectrum disorders</td>
<td>1·05 (0·92-1·20)</td>
<td>1·05 (0·94-1·16)</td>
<td>1·02 (0·95-1·09)</td>
</tr>
<tr>
<td>Depression</td>
<td>1·07 (0·91-1·26)</td>
<td>1·11 (0·97-1·26)</td>
<td>1·10 (1·01-1·19)</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>0·88 (0·76-1·02)</td>
<td>0·99 (0·88-1·11)</td>
<td>1·10 (1·02-1·19)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>1·23 (1·07-1·42)</td>
<td>1·24 (1·11-1·39)</td>
<td>1·15 (1·07-1·24)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>1·19 (1·02-1·39)</td>
<td>1·21 (1·07-1·39)</td>
<td>1·21 (1·11-1·31)</td>
</tr>
<tr>
<td>Drugs redeemed in year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1·33 (1·16-1·54)</td>
<td>1·51 (1·35-1·69)</td>
<td>1·60 (1·48-1·72)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1·13 (0·98-1·30)</td>
<td>1·15 (1·03-1·29)</td>
<td>1·22 (1·13-1·31)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1·33 (1·15-1·53)</td>
<td>1·22 (1·10-1·37)</td>
<td>1·34 (1·25-1·44)</td>
</tr>
</tbody>
</table>
Born in Denmark after January 1, 1955, and diagnosed with schizophrenia for the first time between January 1, 1996 and December 31, 2006.  
$N = 9332$

First schizophrenia diagnosis before age 18.  
$N = 563$

First schizophrenia diagnosis at 18 years or older.  
$N = 8769$

Dead during first in-patient schizophrenia contact.  
$N = 15$

Alive at first psychiatric discharge.  
$N = 8754$

Clozapine redeemed prior to first schizophrenia diagnosis.  
$N = 130$

First clozapine redeemed after first schizophrenia diagnosis.  
$N = 8624$
<table>
<thead>
<tr>
<th>CRITERIA INDICATING TRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
</tr>
<tr>
<td>”Clozapine initiation”</td>
</tr>
<tr>
<td>The date on which the first clozapine prescription was redeemed at the pharmacy after first schizophrenia diagnosis.</td>
</tr>
<tr>
<td>(ii)</td>
</tr>
<tr>
<td>”Eligible for clozapine”</td>
</tr>
<tr>
<td>Psychiatric hospitalization with a schizophrenia diagnosis within 18 months after having had two periods of at least 6 weeks duration with different non-clozapine antipsychotic monotherapies.</td>
</tr>
<tr>
<td>(iii)</td>
</tr>
<tr>
<td>”90-day polypharmacy”</td>
</tr>
<tr>
<td>At least 90-days overlap of periods of two or more different antipsychotics.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRS PROXY DEFINITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>”Clozapine only”</td>
</tr>
<tr>
<td>(i)</td>
</tr>
<tr>
<td>Clozapine initiation</td>
</tr>
<tr>
<td>”TRS main”</td>
</tr>
<tr>
<td>(i) or (ii)</td>
</tr>
<tr>
<td>Clozapine initiation or eligible for clozapine.</td>
</tr>
<tr>
<td>”TRS including polypharmacy”</td>
</tr>
<tr>
<td>(i) or (ii) or (iii)</td>
</tr>
<tr>
<td>Clozapine initiation, eligible for clozapine, or 90-day polypharmacy.</td>
</tr>
</tbody>
</table>
Cumulative incidence of TRS

By sex

By age group

By beddays in previous year

By urbanicity
Necessary Additional Data

Click here to download Necessary Additional Data: Figure and Table legends and footnotes.docx
Aarhus, December 7, 2015.

Dear Reviewers,

Thank you very much for your effort in reviewing this paper and for providing valuable comments. I am pleased to hear that you are now satisfied with my responses and the revised version. I think you were very specific in addressing your comments in the first review, and the manuscript indeed has improved after revising according to your suggestions. Please see my specific responses below.

Best regards,

Theresa Wimberley

Reviewers’ comments:

Reviewer #1: The revised version has shown sound conceptual, methodological and operational credits of the study. My comments were appropriately addressed. I was enjoying reading the text.

Response: Thank you. Thank you very much for reviewing the paper thoroughly and pointing out important points that needed elaboration.

Reviewer #5: From my Point of view, no further concerns appeared, no further revisions seem necessary. I think the paper might be accepted in the present form.

Response: Thank you very much for your valuable comments, which improved the paper, in particular regarding the presentation and discussion of the limitations.