AARHUS UNIVERSITY

Coversheet

This is the accepted manuscript (post-print version) of the article.

Contentwise, the post-print version is identical to the final published version, but there may be differences in typography and layout.

How to cite this publication

Please cite the final published version:

Wimberley, T., Støvring, H., Sørensen, H. J., Horsdal, H. T., MacCabe, J. H., & Gasse, C. (2016). Predictors of treatment resistance in patients with schizophrenia: a population-based cohort study. *Lancet, Psychiatry*, 3(4), 358–366. DOI: [10.1016/S2215-0366\(15\)00575-1](https://doi.org/10.1016/S2215-0366(15)00575-1)

Publication metadata

Title:	Predictors of treatment resistance in patients with schizophrenia: a population-based cohort study
Author(s):	Wimberley, T., Støvring, H., Sørensen, H. J., Horsdal, H. T., MacCabe, J. H., & Gasse, C.
Journal:	Lancet, Psychiatry
DOI/Link:	https://doi.org/10.1016/S2215-0366(15)00575-1
Document version:	Accepted manuscript (post-print)

General Rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Word count (abstract): 233

Word count (text body): 3277

Number of figures: 3

Number of tables: 2

Number of web-tables: 4

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

Authors: Theresa Wimberley, MSc¹, Henrik Støvring, PhD², Holger J Sørensen, PhD^{3,4}, Henriette T Horsdal, PhD¹, James H MacCabe, PhD^{5*}, Christiane Gasse, PhD^{1,6*}

¹*National Centre for Register-based Research, School of Business and Social Sciences, Aarhus University, Fuglesangs allé 4, DK-8210 Aarhus V, Denmark*

²*Section of Biostatistics, Department of Public Health, Aarhus University, Bartholins Allé 2, DK-8000 Aarhus C, Denmark*

³*Research unit , Mental Health Centre Copenhagen, Faculty of Health Sciences, University of Copenhagen, Kildegaardsvej 28, DK-2900 Gentofte, Denmark*

⁴*The Lundbeck Foundation Initiative for Integrative Psychiatric research, iPSYCH, Aarhus University*

⁵*Department of Psychosis Studies, Institute of Psychiatry Psychology and Neuroscience, King's College London, UK*

⁶ *Centre for Integrated Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark*

** Authors contributed equally*

Correspondence and reprint requests should be forwarded to:

Theresa Wimberley, National Centre for Register-based Research, School of Business and Social Sciences, Aarhus University, Fuglesangs allé 4, Building K, DK-8210 Aarhus V, Phone: +45 87165976, e-mail: tw@econ.au.dk

Abstract

BACKGROUND Identification of patients at high risk of treatment-resistant schizophrenia (TRS) at the time of diagnosing schizophrenia would be of great clinical benefit when considering clozapine treatment earlier for patients unlikely to respond to non-clozapine antipsychotics. Knowledge about TRS predictors is limited. Using a treatment-based proxy for TRS, we aimed to identify candidate predictors of TRS at first hospital contact with a schizophrenia diagnosis.

METHODS Using Danish National registry data we conducted a population-based cohort study among all adult patients with incident schizophrenia between January 1, 1996 and December 31, 2006 followed until 31 December, 2010. As main TRS proxy definition we considered the earliest instance of either (i) clozapine initiation or (ii) hospitalization for schizophrenia after having had two periods of different antipsychotic monotherapy. We performed multivariable Cox proportional hazards regression analysis.

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.

FUNDING The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 279227. The funding agency has had no impact in any aspect of data review, interpretation and manuscript writing.

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 guidelines². Compared with the estimated prevalence of TRS of 30%, the prevalence of clozapine prescription varies from 2-3% in parts of the US³, to nearly 60% in China^{3 and 4} with around 10% in most Western European countries including Denmark⁵. 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 outcomes¹². 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 schizophrenia¹⁴⁻¹⁷ 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 their first schizophrenia diagnosis (see figure 1).²⁵

Figure 1 approximately here

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 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 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 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).³² 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).

<i>Table 1 approximately here</i>

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, 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, and 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.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.³⁵ 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.³⁶

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, and 33} 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., 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, and 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 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.

Acknowledgement

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 279227. The funding agency has had no impact in any aspect of data review, interpretation and manuscript writing. We thank Mr. Aske Astrup for contributing to discussions concerning the study design, data management, and analyses.

Reference List

- (1) Barnes TR. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2011;25(5):567-620.
- (2) National Collaborating Centre for Mental Health (UK). Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care (Update). NICE Clinical Guidelines, No. 82. Leicester (UK), British Psychological Society. 2009.
- (3) Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Geographic and Clinical Variation in Clozapine Use in the United States. *Psychiatr Serv* 2014;65(2):186-92.
- (4) Tan CH, Shinfuku N, Sim K. Psychotropic prescription practices in east Asia: looking back and peering ahead. *Curr Opin Psychiatry* 2008;21(6):645-50.
- (5) Nielsen J, Roge R, Schjerning O, Sorensen HJ, Taylor D. Geographical and temporal variations in clozapine prescription for schizophrenia. *Eur Neuropsychopharmacol* 2012;22(11):818-24.
- (6) Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013;382(9896):951-62.
- (7) Novick D, Haro JM, Suarez D, Vieta E, Naber D. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. *Schizophr Res* 2009;108(1-3):223-30.
- (8) Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry* 2012;201(6):481-5.
- (9) Gee S, Vergunst F, Howes O, Taylor D. Practitioner attitudes to clozapine initiation. *Acta Psychiatr Scand* 2014;130(1):16-24.
- (10) Kane JM, Correll CU. Pharmacologic treatment of schizophrenia. *Dialogues Clin Neurosci* 2010;12(3):345-57.
- (11) Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol* 2014;29(2):63-76.
- (12) Harris MG, Henry LP, Harrigan SM, Purcell R, Schwartz OS, Farrelly SE, et al. The relationship between duration of untreated psychosis and outcome: an eight-year prospective study. *Schizophr Res* 2005;79(1):85-93.
- (13) Carbon M, Correll CU. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. *Dialogues Clin Neurosci* 2014;16(4):505-24.
- (14) Agerbo E, Byrne M, Eaton WW, Mortensen PB. Marital and labor market status in the long run in schizophrenia. *Arch Gen Psychiatry* 2004;61(1):28-33.

- (15) Laursen TM, Munk-Olsen T, Nordentoft M, Bo MP. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a danish population-based cohort. *J Clin Psychiatry* 2007;68(11):1673-81.
- (16) Pedersen CB, Mortensen PB. Family history, place and season of birth as risk factors for schizophrenia in Denmark: a replication and reanalysis. *Br J Psychiatry* 2001;179:46-52.
- (17) Thorup A, Waltoft BL, Pedersen CB, Mortensen PB, Nordentoft M. Young males have a higher risk of developing schizophrenia: a Danish register study. *Psychol Med* 2007;37(4):479-84.
- (18) Huber CG, Naber D, Lambert M. Incomplete remission and treatment resistance in first-episode psychosis: definition, prevalence and predictors. *Expert Opin Pharmacother* 2008;9(12):2027-38.
- (19) Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39(7 Suppl):22-5.
- (20) Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011;39(7 Suppl):54-7.
- (21) Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(7 Suppl):30-3.
- (22) Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(7 Suppl):38-41.
- (23) Jensen VM, Rasmussen AW. Danish Education Registers. *Scand J Public Health* 2011;39(7 Suppl):91-4.
- (24) Kyvsgaard B. *The Criminal Career*. Cambridge: Cambridge University Press; 1998.
- (25) Nielsen PR, Laursen TM, Mortensen PB. Association between parental hospital-treated infection and the risk of schizophrenia in adolescence and early adulthood. *Schizophr Bull* 2013;39(1):230-7.
- (26) Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;45(9):789-96.
- (27) Glenthøj B, Gerlach J, Licht R, Gulmann N, Jørgensen OS. Behandling med antipsykotika. Vejledende retningslinjer. [Treatment with antipsychotics. Guidelines] Dansk Psykiatrisk Selskab [Danish Psychiatric Association] 1998.
- (28) Damkier P, Larsen JT, Rasmussen S, Nielsen B, Hansen VH. Kliniske retningslinier for behandling med antipsykotika. [Clinical guidelines for treatment with antipsychotics] Skizofrenisektoren, Psykiatrisk afdeling, Odense Universitetshospital. [Section for schizophrenia, Department of Psychiatry, Odense University Hospital] 2007.
- (29) Fink-Jensen A, Rasmussen I, Viuff AG, Larsen JT, Schmidt M, Peacock L, et al. Behandlingsvejledning inklusiv lægemiddelrekommandation for medicinsk behandling af psykotiske tilstande hos voksne. [Treatment Guidelines including recommendations for medical treatment of psychoses in adults] RADS - Rådet for Anvendelse af Dyr Sygehusmedicin. [The Council for Utilization of Expensive Drugs] 2014.

- (30) Suzuki T, Remington G, Mulsant BH, Uchida H, Rajji TK, Graff-Guerrero A, et al. Defining treatment-resistant schizophrenia and response to antipsychotics: a review and recommendation. *Psychiatry Res* 2012;197(1-2):1-6.
- (31) Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry* 2014;71(5):573-81.
- (32) Baandrup L, Allerup P, Nordentoft M, Lublin H, Glenthøj BY. Exploring regional variation in antipsychotic coprescribing practice: a Danish questionnaire survey. *J Clin Psychiatry* 2010;71(11):1457-64.
- (33) Manuel JJ, Essock SM, Wu Y, Pangilinan M, Stroup S. Factors associated with initiation on clozapine and on other antipsychotics among Medicaid enrollees. *Psychiatr Serv* 2012;63(11):1146-9.
- (34) Vassos E, Pedersen CB, Murray RM, Collier DA, Lewis CM. Meta-analysis of the association of urbanicity with schizophrenia. *Schizophr Bull* 2012;38(6):1118-23.
- (35) Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry* 2012;169(11):1203-10.
- (36) Selten JP, van d, V, Rutten BP, Cantor-Graae E. The social defeat hypothesis of schizophrenia: an update. *Schizophr Bull* 2013;39(6):1180-6.
- (37) Schneider C, Papachristou E, Wimberley T, Gasse C, Dima D, MacCabe JH, et al. Clozapine use in childhood and adolescent schizophrenia: A nationwide population-based study. *Eur Neuropsychopharmacol* 2015;25(6):857-63.
- (38) Wheeler AJ, Feetam CL, Harrison J. Pathway to clozapine use: a comparison between a patient cohort from New Zealand and a cohort from the United Kingdom. *Clin Drug Investig* 2014;34(3):203-11.

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.

CRITERIA INDICATING TRS		
(i)	(ii)	(iii)
"Clozapine initiation"	"Eligible for clozapine"	"90-day polypharmacy"
The date on which the first clozapine prescription was redeemed at the pharmacy after first schizophrenia diagnosis.	Psychiatric hospitalization with a schizophrenia diagnosis within 18 months after having had two periods ^a of at least 6 weeks duration with different non-clozapine antipsychotic monotherapies.	At least 90-days overlap of periods ^a of two or more different antipsychotics.
TRS PROXY DEFINITIONS		
"Clozapine only"	"TRS main"	"TRS including polypharmacy"
(i)	(i) or (ii)	(i) or (ii) or (iii)
Clozapine initiation	Clozapine initiation or eligible for clozapine.	Clozapine initiation, eligible for clozapine, or 90-day polypharmacy.

Cumulative incidence of TRS

Cumulative incidence of TRS

By sex

By age group

By beddays in previous year

By urbanicity

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

	Criteria									
	(i) Clozapine initiation		(ii) Eligible for clozapine		(iii) 90-day polypharmacy		Others not meeting criteria (i), (ii), or (iii)		All diagnosed with schizophrenia	
	n	%	n	%	n	%	n	%	n	%
Total, n (%)	1137	13.2%	990	11.5%	3773	43.8%	4470	51.8%	8624	100%
Patient-related factors										
Female sex vs. male sex	478	42.0%	458	46.3%	1564	41.5%	1537	34.4%	3248	37.7%
Age at first SZ diagnosis, median (IQR)	26.4 (22.1-32.4)		27.3 (22.5-34.5)		28.2 (23.1-35.2)		29.7 (23.7-36.5)		28.9 (23.4-35.8)	
Age										
18-24 years	479	42.1%	383	38.7%	1330	35.3%	1373	30.7%	2844	33.0%
25-34 years	457	40.2%	370	37.4%	1462	38.7%	1770	39.6%	3379	39.2%
35-52 years	201	17.7%	237	23.9%	981	26.0%	1327	29.7%	2401	27.8%
Family history of SZ vs. not (N=8269)	70	6.4%	68	7.2%	265	7.3%	314	7.3%	615	7.4%
Season of birth (Born Dec-March)	366	32.2%	336	33.9%	1235	32.7%	1502	34.0%	2883	33.4%
Paternal age, median (IQR) (N=8388)	29.0 (25.2-33.1)		28.7 (25.1-33.1)		28.7 (25.3-33.4)		29.2 (25.4-33.9)		29.0 (25.2-33.7)	
Early parental loss	80	7.0%	77	7.8%	318	8.4%	311	7.0%	655	7.6%
Living alone vs. couple (N=8558)	570	50.2%	512	51.8%	2007	53.3%	2447	55.5%	465	54.3%
Violent offence	138	12.1%	124	12.5%	445	11.8%	579	13.0%	1067	12.4%
Primary education vs. higher (N=8389)	687	61.9%	614	63.4%	2374	64.7%	2487	57.2%	5071	60.4%
Employment status (N=8620)										
In work	345	30.3%	278	28.1%	1043	27.6%	1444	32.3%	2613	30.3%
Outside working force	561	49.3%	495	50.0%	1803	47.8%	2072	46.4%	4054	47.0%
Unemployed	84	7.4%	69	7.0%	285	7.6%	424	9.5%	742	8.6%
Long-term disability benefit	147	12.9%	148	14.9%	642	17.0%	526	11.8%	1211	14.0%
Urbanicity (Place of living at time of first SZ diagnosis)										
Capital area (capital and suburb to the capital)	308	27.1%	254	25.7%	1073	28.4%	1913	42.8%	3103	36.0%
Provincial area (>10000 inhabitants)	556	48.9%	484	48.9%	1717	45.5%	1763	39.4%	3666	42.5%
Rural area	273	24.0%	252	25.5%	983	26.1%	794	17.8%	1855	21.5%
Disease-related factors										
Bed days at psychiatric hospitals in year prior to first SZ diagnosis										
0 days	574	50.5%	495	50.0%	2129	56.4%	3155	70.6%	5499	63.8%
1-30 days	200	17.6%	202	20.4%	699	18.5%	683	15.3%	1450	16.8%
>30 days	363	31.9%	293	29.6%	945	25.0%	632	14.1%	1675	19.4%
In-patient at first SZ diagnosis	747	65.7%	634	64.0%	2089	55.4%	1788	40.0%	4125	47.8%
Paranoid subtype at first SZ diagnosis	644	56.6%	559	56.5%	206	54.6%	2307	51.6%	459	53.2%
<i>Prior psychiatric diagnoses</i>										
SZ affective disorder	67	5.9%	53	5.4%	190	5.0%	124	2.8%	336	3.9%
Other SZ spectrum disorders	547	48.1%	488	49.3%	1791	47.5%	1796	40.2%	3771	43.7%
Bipolar disorder	43	3.8%	48	4.8%	159	4.2%	161	3.6%	341	4.0%
Depression	259	22.8%	258	26.1%	859	22.8%	666	14.9%	1596	18.5%
Autism	19	1.7%	12	1.2%	52	1.4%	51	1.1%	107	1.2%
Attention Deficit Hyperactivity Disorder	4	0.4%	5	0.5%	27	0.7%	33	0.7%	60	0.7%
Substance abuse (including alcohol, cannabis, and smoking use disorders)	365	32.1%	378	38.2%	1312	34.8%	1221	27.3%	2650	30.7%
Personality disorder	434	38.2%	413	41.7%	1355	35.9%	1055	23.6%	2525	29.3%
Suicide attempt	304	26.7%	301	30.4%	981	26.0%	675	15.1%	1727	20.0%
<i>Drugs redeemed in previous year</i>										
Antipsychotics	644	56.6%	612	61.8%	2155	57.1%	1555	34.8%	3901	45.2%
Antidepressants	449	39.5%	421	42.5%	153	40.6%	1196	26.8%	2846	33.0%
Benzodiazepines	508	44.7%	432	43.6%	1648	43.7%	1197	26.8%	2984	34.6%

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.

	Clozapine only		TRS main		TRS including polypharmacy	
Number of events	1071		1703		3878	
Total person-time at risk (years)	65 657		61 421		47 395	
Rate per 100 person-years	1.62		2.77		8.19	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Patient-related factors						
Female sex versus male sex	1.00	(0.87-1.14)	1.07	(0.96-1.19)	1.04	(0.97-1.12)
Age at first SZ diagnosis	0.94	(0.93-0.95)	0.96	(0.95-0.97)	0.98	(0.97-0.98)
Family history of SZ versus not (n=8269)	0.92	(0.72-1.18)	1.00	(0.83-1.21)	1.03	(0.91-1.17)
Season of birth (Born Dec-March)	0.96	(0.84-1.09)	1.01	(0.91-1.11)	0.97	(0.90-1.03)
Paternal age (n=8388)	1.00	(0.99-1.01)	1.00	(0.99-1.01)	1.00	(0.99-1.00)
Early parental loss	0.88	(0.69-1.12)	0.97	(0.81-1.16)	1.16	(1.03-1.30)
Living alone versus couple	0.99	(0.88-1.12)	1.00	(0.91-1.11)	1.01	(0.95-1.08)
Violent offence	1.12	(0.91-1.37)	1.04	(0.89-1.23)	0.92	(0.82-1.02)
Primary education level versus higher (n=8389)	0.83	(0.72-0.95)	0.88	(0.79-0.98)	1.09	(1.01-1.17)
Employment status (n=8620)						
In work	1		1		1	
Outside working force	0.95	(0.83-1.10)	1.01	(0.90-1.13)	1.06	(0.98-1.14)
Unemployed	0.86	(0.67-1.09)	0.95	(0.79-1.15)	0.94	(0.83-1.07)
Long-term disability benefit	1.23	(0.98-1.55)	1.14	(0.95-1.36)	1.32	(1.17-1.47)
Urbanicity (Place of living at time of first schizophrenia diagnosis)						
Capital area (capital and suburb to the capital)	1		1		1	
Provincial area (>10-000 inhabitants)	1.40	(1.21-1.63)	1.38	(1.23-1.56)	1.38	(1.27-1.49)
Rural area	1.40	(1.18-1.67)	1.44	(1.25-1.65)	1.61	(1.47-1.76)
Disease-related factors						
Bed days (psyc) in year prior to first schizophrenia diagnosis						
0 days	1		1		1	
1-30 days	1.07	(0.90-1.28)	1.11	(0.96-1.27)	1.04	(0.95-1.14)
>30 days	1.62	(1.38-1.91)	1.54	(1.35-1.75)	1.30	(1.19-1.42)
In-patient at first schizophrenia diagnosis	2.06	(1.81-2.34)	2.07	(1.87-2.29)	1.63	(1.53-1.74)
Paranoid subtype at first schizophrenia diagnosis	1.31	(1.16-1.48)	1.24	(1.13-1.37)	1.15	(1.08-1.23)
<i>Prior psychiatric diagnoses</i>						
SZ affective disorder	1.28	(0.99-1.65)	1.18	(0.95-1.45)	1.14	(0.98-1.31)
Other SZ spectrum disorders	1.05	(0.92-1.20)	1.05	(0.94-1.16)	1.02	(0.95-1.09)
Depression	1.07	(0.91-1.26)	1.11	(0.97-1.26)	1.10	(1.01-1.19)
Substance abuse	0.88	(0.76-1.02)	0.99	(0.88-1.11)	1.10	(1.02-1.19)
Personality disorder	1.23	(1.07-1.42)	1.24	(1.11-1.39)	1.15	(1.07-1.24)
Suicide attempt	1.19	(1.02-1.39)	1.21	(1.07-1.39)	1.21	(1.11-1.31)
<i>Drugs redeemed in year</i>						
Antipsychotics	1.33	(1.16-1.54)	1.51	(1.35-1.69)	1.60	(1.48-1.72)
Antidepressants	1.13	(0.98-1.30)	1.15	(1.03-1.29)	1.22	(1.13-1.31)
Benzodiazepines	1.33	(1.15-1.53)	1.22	(1.10-1.37)	1.34	(1.25-1.44)

Appendix

Table A1: Classification of psychiatric disorders according to WHO international classification of diseases (ICD) version 8 and 10.¹

	ICD-8	ICD-10
Schizophrenia	295·x9 (excl. 295·79)	F20
Schizo-affective disorders	295·79, 295·89	F25
Other SZ spectrum disorders	297·xx, 298·29, 298·39, 298·98, 298·99, 299·04, 299·05, 299·09, 301·83	F21-F24, F28-F29
Bipolar disorders	296·19, 296·39, 298·19	F30-F31
Single and recurrent depressive disorder	296·09, 296·29, 298·09, 300·49	F32-F33
Substance abuse including cannabis and smoking use disorders	291·x9, 294·39, 303·x9, 303·20, 303·28, 303·90, 304·x9	F10-F19
Personality disorders	301·x9 excl. 301·19, 301·80-301·82, 301·84	F60
Autism	299·00-299·03	F84
Attention Deficit Hyperactivity Disorder	308·01	F90
Suicide attempt ^a		

^a) Different algorithms were used for different time periods.²

Table A2: Detailed description of TRS proxies and expressions used to derive TRS proxies using registry data.

Main TRS^a outcome definition	TRS is defined as either first CLZ ^a redemption or meeting CLZ eligibility criteria (relapse after two AP ^a periods), whatever comes first. The definition is a proxy for TRS, and is more likely identifying 'probable treatment non-response'.
Alternative definitions of TRS which can be used to evaluate the sensitivity	CLZ initiation only TRS as defined above or 90-day polypharmacy
	Definition
Definition of CLZ eligibility criteria	Psychiatric HX ^a leading to a diagnosis of SZ ^a was used as indication for relapse. The HX should occur between six weeks and 18 months after initiating a second adequate antipsychotic period. The number of adequate AP periods was counted from one year prior to first SZ diagnosis.
Estimated prescription duration	Median distance between prescriptions calculated within patient and ATC ^a group if the patient has at least four redemptions within ATC group. This estimated duration will be replaced by the median distance within ATC group if either the patient has less than four redemptions within a given ATC group or (estimated duration – DDD ^a * number of packages) > 100.
Grace period/maximum allowed gap	100% of the estimated duration of the specific redemption, resulting in a maximum allowed distance between redemptions around the 75 th percentile of the median distance within ATC group.
Duration of a treatment period	Stop-Start, where Start = first redemption Stop = last redemption subsequent redemptions of the same ATC (redeemed within estimated duration + grace period) + estimated duration of the last redemption.
Adequate AP period	Strict AP monotherapy of a period of a duration >= six weeks, i.e. no other AP redemptions for at least six weeks.
Polypharmacy	For the TRS definition including polypharmacy, polypharmacy is defined as concurrent treatment of two or more APs (treatment periods defined as above) for at least 90 days.

^a) TRS = Treatment-Resistant Schizophrenia, CLZ=clozapine, AP = antipsychotic, HX = hospitalization, SZ = schizophrenia, ATC = anatomical therapeutic chemical, DDD = defined daily dose.

Table A3: Hazard rate ratio (HR) and 95% confidence interval (CI) for TRS in a model using the entire follow-up and a model with censoring after two years of follow-up. Estimates are obtained for each candidate predictor in a multivariable model including all listed baseline factors as well as calendar year at first schizophrenia diagnosis, n=8044.

	TRS (entire follow-up)		TRS (censoring after 2 years)	
Number of events	1703		773	
Total person-time at risk (years)	61 421		15 117	
Rate per 100 person-years	2.77		5.07	
	HR	(95% CI)	HR	(95% CI)
Patient-related factors				
Female sex versus male sex	1.07	(0.96-1.19)	1.04	(0.89-1.22)
Age at first SZ diagnosis	0.96	(0.95-0.97)	0.97	(0.96-0.98)
Family history of SZ versus not	1.00	(0.83-1.21)	0.99	(0.74-1.32)
Season of birth (Born Dec-March)	1.01	(0.91-1.11)	0.96	(0.83-1.12)
Paternal age	1.00	(0.99-1.01)	1.00	(0.99-1.01)
Early parental loss	0.97	(0.81-1.16)	0.92	(0.70-1.21)
Living alone versus couple	1.00	(0.91-1.11)	0.97	(0.84-1.13)
Violent offence	1.04	(0.89-1.23)	0.98	(0.77-1.25)
Primary education level versus higher	0.88	(0.79-0.98)	0.92	(0.78-1.08)
Employment status				
In work	1		1	
Outside working force	1.01	(0.90-1.13)	0.97	(0.82-1.16)
Unemployed	0.95	(0.79-1.15)	0.84	(0.61-1.16)
Long-term disability benefit	1.14	(0.95-1.36)	1.11	(0.87-1.43)
Urbanicity (Place of living at time of first SZ diagnosis)				
Capital area (capital and suburb to the capital)	1		1	
Provincial area (>10,000 inhabitants)	1.38	(1.23-1.56)	1.92	(1.58-2.33)
Rural area	1.44	(1.25-1.65)	2.00	(1.60-2.48)
Disease-related factors				
Bed days (psyc) in year prior to first SZ diagnosis				
0 days	1		1	
1-30 days	1.11	(0.96-1.27)	1.25	(1.03-1.53)
>30 days	1.54	(1.35-1.75)	1.66	(1.38-2.00)
In-patient at first SZ diagnosis	2.07	(1.87-2.29)	2.22	(1.91-2.59)
Paranoid subtype at first SZ diagnosis	1.24	(1.13-1.37)	1.21	(1.05-1.40)
<i>Prior psychiatric diagnoses</i>				
SZ affective disorder	1.18	(0.95-1.45)	1.18	(0.89-1.57)
Other SZ spectrum disorders	1.05	(0.94-1.16)	1.04	(0.89-1.21)
Depression	1.11	(0.97-1.26)	1.17	(0.98-1.39)
Substance abuse	0.99	(0.88-1.11)	0.96	(0.81-1.14)
Personality disorder	1.24	(1.11-1.39)	1.28	(1.09-1.50)
Suicide attempt	1.21	(1.07-1.39)	1.19	(1.00-1.42)
<i>Drugs redeemed in year</i>				
Antipsychotics	1.51	(1.35-1.69)	1.98	(1.66-2.36)
Antidepressants	1.15	(1.03-1.29)	1.29	(1.09-1.52)
Benzodiazepines	1.22	(1.10-1.37)	1.47	(1.25-1.73)

Table A4: Hazard rate ratio (HR) and 95% confidence interval (CI) for TRS (main definition, and two alternative definitions estimated for each candidate predictor individually in models including only sex, age and calendar year at first schizophrenia diagnosis, n=8624.

	Clozapine only		TRS main		TRS including polypharmacy	
Number of events	1137		1820		4154	
Total person-time at risk (years)	70 244		65 732		50 692	
Rate per 100 person-years	1.62		2.77		8.19	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Patient-related factors						
Female sex versus male sex	1.26	(1.12-1.42)	1.33	(1.21-1.45)	1.25	(1.18-1.33)
Age at first SZ diagnosis	0.96	(0.95-0.97)	0.97	(0.97-0.98)	0.99	(0.99-0.99)
Family history of SZ versus not (n=8269)	0.87	(0.68-1.10)	0.95	(0.79-1.14)	1.01	(0.89-1.13)
Season of birth (Born Dec-March)	0.97	(0.85-1.09)	1.01	(0.91-1.11)	0.97	(0.91-1.03)
Paternal age (n=8388)	0.99	(0.98-1.00)	1.00	(0.99-1.00)	0.99	(0.99-1.00)
Early parental loss	0.91	(0.73-1.14)	1.02	(0.86-1.21)	1.17	(1.04-1.30)
Living alone versus couple	0.96	(0.88-1.12)	0.97	(0.88-1.06)	0.96	(0.90-1.02)
Violent offence	1.20	(1.00-1.44)	1.23	(1.06-1.42)	1.07	(0.97-1.18)
Primary education level versus higher (n=8389)	0.92	(0.81-1.05)	1.00	(0.90-1.10)	1.23	(1.15-1.32)
Employment status (n=8620)						
In work	1		1		1	
Outside working force	1.00	(0.88-1.15)	1.07	(0.96-1.19)	1.14	(1.06-1.22)
Unemployed	0.83	(0.65-1.05)	0.91	(0.76-1.10)	0.95	(0.84-1.07)
Long-term disability benefit	1.51	(1.23-1.86)	1.45	(1.23-1.70)	1.81	(1.64-2.01)
Urbanicity (Place of living at time of first SZ diagnosis)						
Capital area (capital and suburb to the capital)	1		1		1	
Provincial area (>10,000 inhabitants)	1.59	(1.39-1.83)	1.54	(1.38-1.72)	1.57	(1.46-1.69)
Rural area	1.61	(1.36-1.89)	1.63	(1.44-1.85)	1.87	(1.72-2.04)
Disease-related factors						
Bed days (psyc) in year prior to first SZ diagnosis						
0 days	1		1		1	
1-30 days	1.37	(1.17-1.61)	1.49	(1.31-1.69)	1.42	(1.31-1.54)
>30 days	2.20	(1.93-2.51)	2.15	(1.94-2.39)	1.84	(1.71-1.98)
In-patient at first SZ diagnosis	2.13	(1.88-2.41)	2.13	(1.93-2.34)	1.64	(1.54-1.74)
Paranoid subtype at first SZ diagnosis	1.31	(1.16-1.48)	1.26	(1.15-1.39)	1.15	(1.08-1.22)
<i>Prior psychiatric diagnoses</i>						
SZ affective disorder	1.80	(1.40-2.30)	1.63	(1.33-2.00)	1.65	(1.43-1.89)
Other SZ spectrum disorders	1.31	(1.16-1.47)	1.35	(1.23-1.48)	1.30	(1.22-1.38)
Depression	1.56	(1.35-1.80)	1.57	(1.41-1.76)	1.53	(1.42-1.65)
Substance abuse	1.24	(1.10-1.41)	1.39	(1.27-1.53)	1.47	(1.38-1.57)
Personality disorder	1.62	(1.43-1.83)	1.69	(1.54-1.87)	1.59	(1.49-1.69)
Suicide attempt	1.62	(1.42-1.85)	1.70	(1.53-1.89)	1.73	(1.61-1.86)
<i>Drugs redeemed in year</i>						
Antipsychotics	1.84	(1.64-2.08)	2.01	(1.83-2.21)	2.16	(2.03-2.30)
Antidepressants	1.53	(1.36-1.73)	1.54	(1.40-1.70)	1.65	(1.55-1.76)
Benzodiazepines	1.85	(1.64-2.09)	1.78	(1.62-1.95)	1.93	(1.81-2.06)

Reference List

- (1) Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, et al. A Comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *Jama Psychiatry* 2014;71(5):573-81.
- (2) Webb RT, Antonsen S, Mok PL, Agerbo E, Pedersen CB. National cohort study of suicidality and violent criminality among danish immigrants. *Plos One* 2015;10(6):e0131915.