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Inverse association between Urbanicity and Treatment Resistance in Schizophrenia

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Abstract: 232

Text: 2932

Tables: 2

Figures: 2

Supplementary material: 3

Abstract

Background: Living in a larger city is associated with increased risk of schizophrenia; and world-wide, consistent evidence shows that the higher the degree of urbanicity the higher the risk of schizophrenia. However, the association between urbanicity and treatment-resistant schizophrenia (TRS) as a more severe form of schizophrenia or separate entity of schizophrenia has not been fully explored yet. We aimed to investigate the association between urbanicity and incidence of TRS.

Methods: A large Danish population-based cohort of all individuals with a first schizophrenia diagnosis after 1996 was followed until 2013 applying survival analysis techniques. TRS was assessed using a treatment-based proxy, defined as the earliest observed instance of either clozapine initiation or hospital admission due to schizophrenia after having received two prior antipsychotic monotherapy trials of adequate duration.

Results: Among the 13,349 schizophrenia patients, 17.3% experienced TRS during follow-up (median follow-up 7 years, inter-quartile range: 3-12 years). The 5-year risk of TRS ranged from 10.5% in the capital area to 17.6% in the rural areas. Compared with individuals with schizophrenia residing in the capital area, hazard ratios were 1.44 (1.31-1.59) for provincial areas and 1.60 (1.43-1.79) for rural areas.

Conclusion: Higher rates of TRS were found in less urbanized areas. The different direction of urban-rural differences regarding TRS and schizophrenia risk may indicate urban-rural systematic differences in treatment practices or different urban-rural etiologic types of schizophrenia.

Keywords: schizophrenia, treatment resistance, urbanicity, antipsychotics, clozapine

1 Introduction

The association between urbanicity and schizophrenia has been extensively studied, and consistently an increased incidence of schizophrenia has been observed at higher levels of urbanicity (March et al., 2008; Pedersen and Mortensen, 2001b; Vassos et al., 2012; Vassos, 2015). This finding was invariant to the definition used for urban exposure (population size or density); whether urbanicity was determined at birth, upbringing, schizophrenia diagnosis, or interview; and whether based on cohort or cross-sectional study designs (March et al., 2008; Pedersen, 2006, 2015; Pedersen and Mortensen, 2001a; Torrey et al., 1997).

Treatment resistant schizophrenia (TRS) is generally defined as not responding adequately to treatment despite at least two first-line antipsychotic treatments. It is a clinically relevant complication of the course of schizophrenia affecting approximately 30% of all persons with schizophrenia. TRS is [burdened with heavy reductions in](#) life quality and [high](#) costs of medication and health services (Barnes, 2011; Kennedy et al., 2013).

It is [debated](#) whether TRS merely constitutes the most severe end of spectrum of schizophrenia or if it defines a distinct subtype of schizophrenia. The latter may suggest a different etiology of TRS than of schizophrenia; in that sense, urbanicity would be hypothesized to act differently in TRS. This hypothesis was supported by a recent study reporting an increased incidence of TRS at lower levels of urbanicity compared to higher levels of urbanicity (Wimberley et al., 2016). This association merits closer investigation in an etiological setting adjusting for an appropriately chosen set of confounders and evaluating [its temporal](#) association. This could help elucidate the nature and course of schizophrenia and predict TRS. A better understanding of urban-rural differences in TRS may be helpful to optimize treatment for patients with TRS and thereby improve treatment outcomes. Utilizing the nationwide longitudinal information on all individuals with schizophrenia recorded in Danish registers, we therefore aim to assess the association between urbanicity and a treatment-based proxy for TRS. Moreover, we aim to evaluate the [temporal](#) association between urbanicity and TRS.

2 Methods

2.1 Study cohort

We conducted a population-based cohort study including all individuals born in Denmark after 1955 with a first diagnosis of schizophrenia (ICD-10: F20) between January 1, 1996 and July 1, 2013 and aged 18 years or older. We excluded individuals who received clozapine prior to their first recorded schizophrenia diagnosis, or died or emigrated during their first admission to a psychiatric hospital with a schizophrenia

diagnosis. We followed individuals from their first diagnosis of schizophrenia until criteria were met for TRS, emigration from Denmark, death, or July 1, 2013 ([whichever came first](#)).

2.2 Data sources

We extracted information on all prescriptions redeemed at a pharmacy from The Danish National Prescription Registry, where all drug prescriptions since 1995 have been registered (Kildemoes et al., 2011). We obtained information on hospital admission dates and diagnoses (WHO International Classification of Diseases (ICD) version 8 and 10) both from the Danish Psychiatric Central Research Register and from the Danish National Patient Registry (Mors et al., 2011; Lyngø et al., 2011). We obtained information on sex, date of birth, as well as current and past residence in Denmark from the Danish Civil Registration System established in 1968 (Pedersen, 2011). The unique personal identification number was used to link individual data across the national registration systems, including registers holding socio-demographic information (Jensen and Rasmussen, 2011).

2.3 Treatment-resistant schizophrenia

We defined occurrence of TRS from data on prescriptions and psychiatric admissions based on Danish treatment guidelines and clinical practice (Damkier et al., 2009, Glenthøj et al., 1998). Our proxy definition was adapted from the definition of Kane and colleagues and reflected previous and current Danish and international treatment guidelines (National Collaborating Centre for Mental Health (UK), 2009; Damkier et al., 2009; Kane et al., 1988; Suzuki et al., 2012). In Denmark, clozapine should be considered prescribed by the psychiatrist in case of insufficient treatment response for at least two antipsychotic medications prescribed as monotherapy. Patients are monitored with weekly ECG during dosage titration and ECG monitoring continues once stable dosage has been reached. Weekly blood monitoring is required the first 18 weeks after initiation, followed by monthly blood monitoring. In epidemiological population-based studies, clozapine is often used as a proxy for TRS. However, clozapine is often underprescribed, probably due to the regular monitorings and the fear of severe side effects. Thus, we extended the definition of TRS to include patients meeting eligibility criteria for clozapine. Individuals met the TRS proxy criteria at their earliest observed instance of either (1) redemption of a clozapine prescription or (2) meeting the eligibility criteria for clozapine, defined as a hospital admission with a diagnosis of schizophrenia with evidence of treatment adherence after having received two prior antipsychotic monotherapy trials of adequate duration, counted from one year prior to the first recorded schizophrenia diagnosis.

Antipsychotic treatment was defined by prescriptions with ATC codes N05A, excluding N05AN01 (lithium). See table A1 in supplementary material for more detailed description.

2.4 Urbanicity

The degree of urbanicity – based on place of residence – was classified into three levels: 1) capital area, 2) provincial area, and 3) rural area, as previously reported (Vassos, 2015; Pedersen, 2006).

2.5 Statistical methods

We analyzed the association between levels of urbanicity at time of first diagnosis of schizophrenia and time to TRS reporting hazard rate ratios (HR) and 95% confidence intervals (CI) from Cox proportional hazards regression analysis. **For each sex, time since first diagnosis of schizophrenia was the time scale.**

We calculated estimates in two models; one model only adjusted for age and calendar year of first schizophrenia diagnosis, and a model **also** adjusted for other socio-demographic and disease-related baseline factors (Table 1).

Cumulative incidences were plotted stratified by urbanicity and were based on a competing risks model with death as well as emigration from Denmark as a competing event. Ignoring censoring from emigration and death may bias the cumulative incidences (Andersen et al., 2012).

To examine the **temporal association between** exposure and outcome, we conducted the following secondary analyses: First, we estimated the interaction between urbanicity at diagnosis and year since diagnosis, i.e. estimates for TRS occurring in different years of follow-up, where the follow-up **time was** split into five one-year **calendar-year bands**???. Furthermore, we conducted analyses assessing urbanicity at various ages from birth to the 18th birthday (age 0, 2, 4, ..., 18), and urbanicity assessed in every year five years prior to the diagnosis of schizophrenia.

Please note, that for analyses where urbanicity was assessed at birth or during the first 18 years after birth, we restricted the study cohort to individuals born after January 1, 1971 as information on residence was not available before 1971 (Pedersen et al., 2006).

The assumption of proportional hazards for the variables urbanicity and sex was tested by log-log plots and by testing for significant time-dependent effects. The log-log plots indicated no major violations of the proportional hazards assumptions for urbanicity, **but a statistically significant time-dependent effect was found for the variable sex. To account for this we allowed different baseline hazards for males and females.** Moreover, all estimates were adjusted for age and calendar year at first diagnosis. Statistical analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX, USA), except for cumulative incidences which were calculated and plotted using R Statistical Software version 3.1.2. All statistical tests used a two-sided alpha of 5%. All estimates are accompanied by 95% likelihood-ratio based confidence intervals.

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We conducted several sensitivity analyses to investigate the robustness of the results. First, we used the more narrow TRS proxy definition of clozapine initiation only. Although clozapine is underprescribed and this definition will not capture all being treatment resistant, it is likely to have a high positive predictive value since almost all patients on clozapine meet criteria for treatment resistance. Second, to account for the fact that more than 50% redeemed antipsychotics prior to their first recorded diagnosis of schizophrenia, which may – by definition of the outcome – bias the results, we restricted the analysis to individuals who initiated antipsychotics after their first recorded diagnosis of schizophrenia. Third, the main analysis was repeated using the following five-level categorization of the urbanicity exposure (capital, suburb to the capital, provincial city, provincial town, and rural area). Last, all-cause mortality was evaluated as a proxy for disease severity across levels of urbanicity.

3 Results

Among the 13,349 individuals with their first schizophrenia diagnosis between January 1, 1996 and July 1, 2013, a total number of 2313 (17.3%) met at least one of the two criteria for TRS. In particular, 1424 (10.7%) redeemed at least one clozapine prescription (criterion one) and 1281 (9.6%) were admitted to hospital after two periods of different antipsychotic monotherapy (criterion two). Median follow-up was 7 years, inter-quartile range: 3-12 years. A significant urban-rural difference in absolute risk of TRS was estimated at 5 and 10 years after first schizophrenia diagnosis; at 5 years the risk ranged from 10.5% in the capital area to 17.6% in the rural areas (Figure 1 and Table 2). Distributions of baseline characteristics across levels of urbanicity at first diagnosis of schizophrenia are shown in Table 1. Most factors were not equally distributed across levels of urbanicity, and in particular a higher prevalence of individuals with prior psychotropic medication as well as other medication was present in the provincial and rural areas.

Table 1 approximately here

We found a clear association between lower levels of urbanicity (at diagnosis) and increased incidence of TRS. Hazard ratio estimates (HR) were (capital area as reference): HR=1.44 (1.31-1.59) for provincial areas and HR=1.60 (1.43-1.79) for rural areas (Table 2). The effect sizes remain significant when including socio-demographic and disease-related baseline factors in the model (Table 2).

Table 2 approximately here

The cumulative incidence of TRS is shown in [Figure 2](#). The cumulative incidence measures the probability of meeting the TRS criteria before a given time since the first recorded diagnosis of schizophrenia. [Figure 2](#) shows that irrespectively of time since first schizophrenia diagnosis, individuals living in less urban areas than the capital have the highest risk of meeting the TRS criteria.

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The effect of urbanicity was even larger when TRS occurred in the first years after the first schizophrenia diagnosis and the effect diminished when the TRS criteria was met in later years after diagnosis (Figure A1).

When urbanicity at birth (as opposed to urbanicity at diagnosis) was used as exposure, the rate of TRS remained higher in provincial and rural areas compared to the capital area, although with slightly smaller effect sizes only reaching statistical significance for the provincial areas: provincial areas, HR=1.19 (1.05-1.34), rural areas, HR= 1.12 (0.98-1.28).

The urban-rural differences showed a tendency to diminish slightly when urbanicity was assessed at younger age (Figure 2a) or longer before diagnosis of schizophrenia (Figure 2b).

For the clozapine only definition, similar results were found. When urbanicity was obtained at diagnosis, the estimates were (capital area as reference): HR=1.55 (1.36-1.76) for provincial areas and HR=1.63 (1.41-1.88) for rural areas (Table A3). When urbanicity was obtained at birth, the estimates were: HR=1.18 (1.02-1.38), rural areas, HR= 1.17 (0.99-1.38). For urbanicity obtained at different time points between birth and diagnosis of schizophrenia, and for TRS occurring in different years after diagnosis, similar patterns were seen for the clozapine only definition (Figure A2 and A3).

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Results of sensitivity analyses were only reported for the TRS proxy definition including both those initiating clozapine and those meeting eligibility criteria for clozapine. Restricting to individuals only initiating antipsychotic treatment after diagnosis of schizophrenia resulted in similar but decreased effect sizes for urbanicity at diagnosis (capital area as reference: HR=1.22 (1.03-1.44) for provincial areas and HR=1.20 (0.98-1.47) for rural areas) and the years prior to first schizophrenia diagnosis (results not shown, available upon request). For urbanicity obtained at birth and during the first 18 years, no relation between urbanicity and TRS was found among new users of antipsychotics (results not shown, available upon request).

We repeated the analyses categorizing urbanicity exposure using a more detailed 5-level classification as used in a previous study on urbanicity and schizophrenia (Pedersen and Mortensen ,2001b). Estimates were (capital as reference): suburb to the capital, HR=1.34 (1.14-1.58), provincial city, HR=1.65 (1.43-1.91), provincial town, HR=1.60 (1.41-1.82), rural area, HR=1.79 (1.57-2.04).

The cumulative incidence of all-cause mortality after the first diagnosis of schizophrenia was largest in the capital area, whereas provincial areas had the lowest mortality (Figure A2).

4 Discussion

The present study demonstrates that the lower the degree of urbanicity the higher the risk of TRS, irrespective of which point in time urbanicity was measured prior to the first diagnosis of schizophrenia. Based on the worldwide consistent finding that the higher the degree of urbanicity the higher the risk of schizophrenia, our finding was contrary to our expectations.

Our finding is in accordance with a Danish study showing that individuals treated at university hospitals, which are mainly located in the more urban areas of Denmark, are less likely to have clozapine prescribed compared to individuals treated at non-university hospitals mainly located in less urban areas (Nielsen et al., 2012). Another study on predictors of TRS identified the same association between urbanicity obtained at diagnosis and the treatment-based proxy for TRS (Wimberley et al., 2016).

Using residential information on urbanicity provided us with the rare and unique possibility to evaluate the impact of urbanicity on TRS at various time-points, both before and at first diagnosis of schizophrenia. We found that urbanicity acted prior to diagnosis of schizophrenia. However, a decreasing though still significant effect was observed the earlier urbanicity was measured prior to schizophrenia diagnosis, indicating the robustness of the association. With regard to timing of TRS, we only found an effect of urbanicity if TRS occurred within the first two years after diagnosis of schizophrenia, with living in the capital area being associated with decreased TRS compared to any other level of urbanicity, but the effect sizes diminishing with time after diagnosis of schizophrenia. This could to some extent indicate earlier recognition of TRS in rural areas.

4.1 Can regional differences in treatment or diagnostic procedures explain urban-rural differences in TRS?

The results may partly be explained by systematic differences in prescribing practice across different levels of urbanicity. Even though baseline characteristics show that individuals living in the capital are more likely to have prior schizophrenia-like diagnoses, individuals in rural areas are more likely to redeem antipsychotics as well as other psychotropic treatment in the year prior to their first diagnosis of schizophrenia. This may introduce a bias whereby individuals living in rural areas are more likely to fulfil the treatment-based TRS criteria of having previously unsuccessfully received two or more courses of antipsychotic treatment. The effect sizes, however, remained significant though decreased after adjusting for prior antipsychotic use and when restricting to new users of antipsychotic treatment. Moreover, the association between urbanicity at first schizophrenia diagnosis and TRS persisted even when different

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proxy definitions of TRS were applied. Using hospital and prescription registry data it was not possible to investigate why individuals in rural areas initiated antipsychotic treatment earlier than in urban areas, or whether alternative non-pharmacological treatment options were offered in the capital area instead. Furthermore, previous research found shorter duration of untreated psychosis (DUP) to be associated with better prognosis (Harris et al., 2005), and significantly longer DUP was observed in highly urbanized areas in the Netherlands (Boonstra et al., 2012). In our study cohort individuals diagnosed with schizophrenia were not older in rural areas, indicating that detection of schizophrenia does not seem to be delayed in less urban areas.

Moreover, first-time psychosis patients living in rural areas may to a higher extent – due to less access to psychiatric services – be treated by their general practitioners before referral to a psychiatric hospital, where the diagnosis of schizophrenia is for the first time being recorded in the hospital register, our source of information. By contrast the capital area and the second largest city in Denmark participated in an early intervention trial (OPUS) for first-episode psychosis patients, which may have generally affected treatment strategies in these areas (Petersen et al., 2005). Individuals in the capital were more likely to have a prior schizophrenia-like diagnosis, whereas individuals in rural areas were more likely to have a prior diagnosis of bipolar disorder, personality disorder or depression. First, this could indicate differences in diagnostic work-up and treatment before the schizophrenia diagnosis is confirmed. Second, this could indicate different clinical subtypes of schizophrenia in rural versus urban areas.

4.2 Is TRS a distinct subtype of schizophrenia?

Our findings are consistent with an emerging view that TRS is a distinct type of schizophrenia with a different aetiology than treatment-responsive schizophrenia, rather than merely representing a more severe form of schizophrenia (Nakajima et al., 2015, Sagud, 2015). While urbanicity is a well-established risk factor for schizophrenia per se (March et al., 2008; Vassos et al., 2012) it may be that the urban excess in schizophrenia applies only to treatment-responsive schizophrenia and does not apply to TRS. In other words, the association may be better conceptualised as an excess of treatment-responsive schizophrenia in cities as opposed to an excess of treatment-resistant schizophrenia in rural areas.

4.3 Other potential explanations

The association between urbanicity and TRS could also theoretically be explained by migration of pre-schizophrenic or prodromal cases from urban settings to rural areas (Freeman, 1994). However, persons with schizophrenia in Denmark have recently been shown to migrate towards more urban areas due to the development of the disorder or its prodromata (Pedersen, 2015).

Another potential explanation includes increased severity of schizophrenia in urban areas as implicated by the detected excess mortality of schizophrenia in urban areas. However, even if all persons with schizophrenia who lived in the capital at time of first schizophrenia diagnosis and died within 10 years were designated as having developed TRS, this would still not have been sufficient to reach the same level of cumulative incidence of TRS after 10 years as for those diagnosed in a rural area.

4.4 Limitations

Our TRS proxy was defined exclusively from registry data using information on antipsychotic redemptions from community pharmacies and psychiatric hospital admissions. This definition cannot distinguish so-called treatment resistance from insufficient treatment response and switching to clozapine or other antipsychotics due to intolerance or non-adherence. The fact that we do not have information on antipsychotic medication during hospitalization implies potential underestimation of the number of monotherapy trials and thereby underestimation of treatment-resistant cases defined by our proxy for TRS. Furthermore the applied main definition may overestimate the true occurrence of TRS. By contrast, clozapine is often used as a proxy for treatment resistance, as it is considered the most effective antipsychotic treatment (Harris et al. 2005) and it is the only treatment for TRS with a firm evidence base as reflected by official treatment guidelines (National Collaborating Centre for Mental Health (UK), 2009; Leucht et al., 2013; Damkier et al., 2009). Still, many patients with TRS are not treated with clozapine (Howes et al., 2012). We believe that our approach of using clozapine initiation as well as re-admission while treated after having had two periods of different antipsychotic monotherapies with good adherence – although not an exact measure of truly treatment resistance – is the most accurate marker of insufficient treatment response that can be obtained from the available data. We found similar results when restricting to the clozapine initiation only definition, indicating that the different rates of TRS across levels of urbanicity were not restricted to clozapine prescribing or to other antipsychotic use and psychiatric admissions.

4.5 Conclusion

We observed that the lower the degree of urbanization the higher the risk of TRS. This effect was strongest when urbanicity was assessed at time of first diagnosis and when treatment resistance was identified shortly after schizophrenia diagnosis. This inverse finding is intriguing in comparison with the well-known association that the higher the degree of urbanization the higher the risk of schizophrenia. It may indicate systematic differences in treatment practices across different levels of urbanicity, or differences in aetiology between treatment-responsive and treatment-resistant schizophrenia.

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Figure and Table legends and footnotes

Table 1: Baseline characteristics across levels of urbanicity at first schizophrenia diagnosis. n=13,349.

^{a)} The distribution differed significantly across levels of urbanicity.

Table 2: Association between levels of urbanicity at first schizophrenia diagnosis and treatment-resistant schizophrenia (TRS). Hazard rate ratios (HR) and absolute 5- and 10-year risks of TRS are presented. All estimates are accompanied by 95% confidence intervals.

a) Adjusted for age and calendar year of first schizophrenia diagnosis, and allowing different baseline hazards for males and females. N=13,349.

b) Adjusted for age and calendar year of first schizophrenia diagnosis, family history of schizophrenia, education, work status, marital status, prior suicide attempts, prior diagnosis of schizophrenia spectrum disorder, prior diagnosis of other psychiatric disorders, psychiatric hospitalization in previous year, psychotropic drugs (antidepressants or benzodiazepines) redeemed in previous year, and allowing different baseline hazards for males and females. N=12,611.

c) The absolute risk (or cumulative incidence) of TRS at 5 and 10 years after first diagnosis with schizophrenia

Figure 1: Cumulative incidence of TRS stratified by level of urbanicity at first diagnosis of schizophrenia. The cumulative incidence measure the probability (or risk) for a person with schizophrenia of meeting TRS criteria according to number of years since first schizophrenia diagnosis.

Figure 2: Hazard ratio estimates for TRS in different models where urbanicity were obtained at different time points. (a) Ages after birth, where the cohort is restricted to individuals born after 1971 to have full information on residence at time of birth. (b) Years prior to first schizophrenia diagnosis.

Main Tables and Figures

Table 1: Baseline characteristics across levels of urbanicity at first schizophrenia diagnosis. n=13,349.

Baseline characteristics (%)	Levels of urbanicity at diagnosis			
	Capital area	Provincial areas	Rural areas	Total
N (%)	4,394 (32.9%)	5,746 (43.0%)	3,209 (24.0%)	13,349 (100%)
Age, median (inter-quartile range) ^a	28.3 (22.7-36.6)	26.6 (22.1-34.3)	27.5 (21.9-35.9)	27.4 (22.2-35.3)
Age<25 ^a	36.1	42.5	41.9	40.3
Female sex	37.6	39.9	38.8	38.9
Family history of SZ	8.5	7.2	7.7	7.7
Education (only primary level) ^a	57.4	64.9	70.3	63.7
Work status (early ret. pens.) ^a	11.1	15.3	17.9	14.5
Living alone vs. cohabitating ^a	79.1	76.1	67.2	74.9
Suicide attempts prior to diagnosis ^a	16.3	23.4	23.1	21.0
Prior diagnosis of SZ spectrum disorder ^a	50.4	39.9	40.5	43.5
Other prior psychiatric diagnosis than schizophrenia (bipolar, depression, personality disorder, autism, ADHD) ^a	41.6	44.9	47.5	44.4
Prior diagnosis of substance abuse	32.0	31.2	31.7	31.6
Psychiatric hosp. in previous year	30.0	27.9	28.6	28.7
In-patient at first diagnosis	40.6	42.9	42.2	42.0
Psychotropic drugs (antipsychotics, antidepressants, benzodiazepines, or mood stabilizers) redeemed in previous year ^{a, b}	56.1	70.5	74.5	66.7
Any drugs (non-neuroleptics) redeemed in previous year ^a	56.1	60.8	64.8	60.2

^a) The distribution differed significantly across levels of urbanicity.

b) Percentages increase across levels of urbanicity for all four classes of psychotropic drugs. Further details on classification of drugs can be found in table A2 in the appendix.

Table 2: Association between levels of urbanicity at first schizophrenia diagnosis and treatment-resistant schizophrenia (TRS). Hazard rate ratios (HR) and absolute 5- and 10-year risks of TRS are presented. All estimates are accompanied by 95% confidence intervals.

Level of urbanicity (diagnosis)	Total	Number of events	Incidence Rate per 100 person-years	HR and 95% CI for TRS		Absolute risk of TRS after first diagnosis ^c	
				Model 1 ^a	Model 2 ^b	5-year risk (%)	10-year risk (%)
Capital area	4394	608	1.98 (1.83-2.14)	1.00 (ref)	1.00 (ref)	10.5 (9.6-11.6)	15.7 (14.5-17.0)
Provincial areas	5746	1081	2.98 (2.81-3.16)	1.44 (1.31-1.59)	1.40 (1.26-1.56)	17.3 (16.3-18.4)	22.0 (20.7-23.2)
Rural areas	3209	624	3.29 (3.04-3.56)	1.60 (1.43-1.79)	1.56 (1.39-1.76)	17.6 (16.1-19.1)	23.1 (21.3-24.9)

a) Model 1: Adjusted for age and calendar year of first schizophrenia diagnosis, and allowing different baseline hazards for males and females. N=13,349.

b) Model 2: Adjusted for age and calendar year of first schizophrenia diagnosis, family history of schizophrenia, education, work status, marital status, prior suicide attempts, prior diagnosis of schizophrenia spectrum disorder, prior diagnosis of other psychiatric disorders, psychiatric hospitalization in previous year, drugs (antidepressants, benzodiazepines, or mood stabilizers) redeemed in previous year, and allowing different baseline hazards for males and females. N=12,611.

c) The absolute risk (or cumulative incidence) of TRS at 5 and 10 years after first diagnosis with schizophrenia. [To help the average reader I suggest to include: Figure 1 contain identical estimates for all time-points from 0 to 10 years since first diagnosis with schizophrenia.](#)

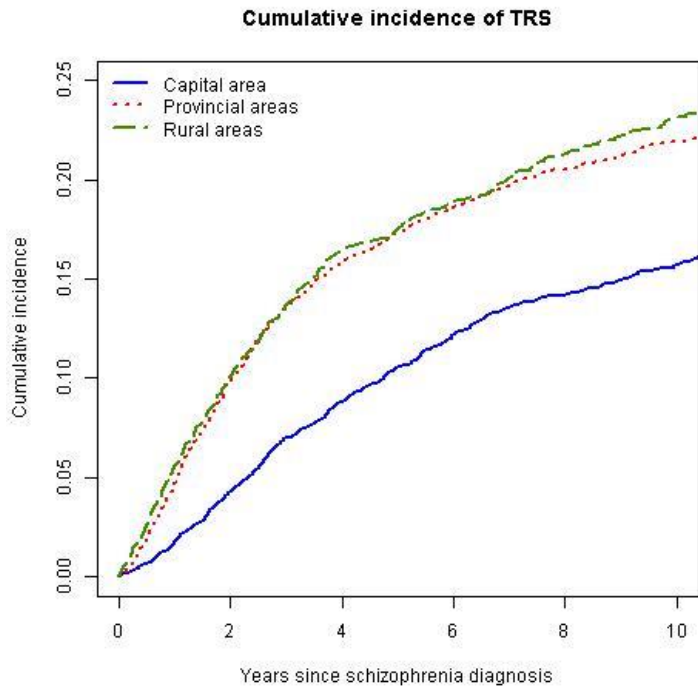


Figure 2: Cumulative incidence of TRS stratified by level of urbanicity at first diagnosis of schizophrenia. The cumulative incidence measure the probability (or risk) for a person with schizophrenia of meeting TRS criteria according to number of years since first schizophrenia diagnosis. [Table 1 contain identical estimates at two selected time points: 5 year risk and 10 year risk.](#)

HRs for TRS for urbanicity at different time points (Capital area as reference)

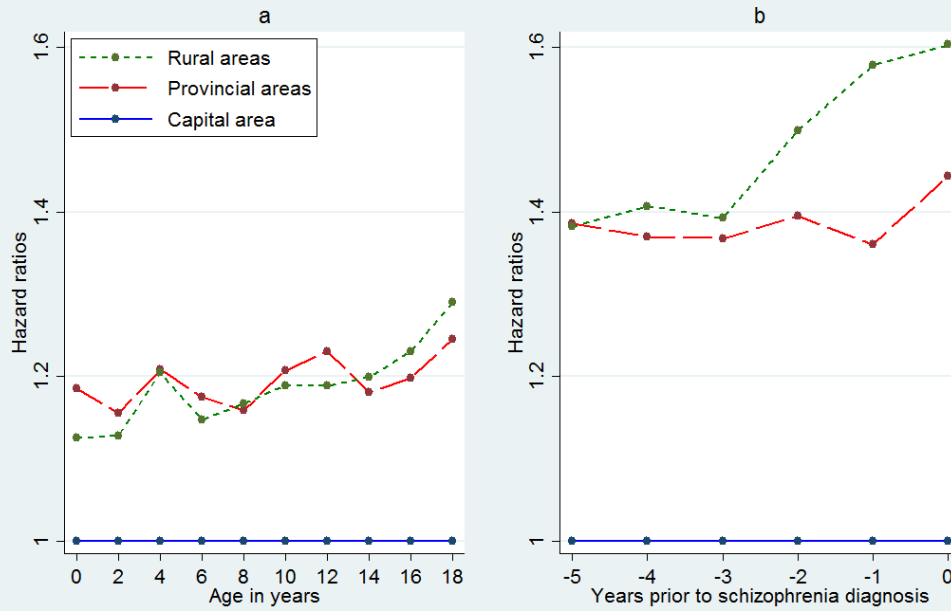


Figure 2: Hazard ratio estimates for TRS in different models where urbanicity were obtained at different time points. (a) Ages after birth, where the cohort is restricted to individuals born after 1971 to have full information on residence at time of birth. (b) Years prior to first schizophrenia diagnosis.