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Inverse association between urbanicity and treatment resistance in schizophrenia

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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 aetiologic types of schizophrenia.

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 aetiology 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 aetiological 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

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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 they met criteria for TRS, emigrated from Denmark, died, or until 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; Lynge 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 sociodemographic information (Jensen and Rasmussen, 2011).

2.3. Treatment-resistant schizophrenia (TRS)

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). In epidemiological population-based studies, 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). In Denmark, psychiatrists should consider prescribing clozapine in case of insufficient treatment response to at least two different sufficiently long antipsychotic monotherapy trials. However, clozapine is assumed to be underprescribed, probably due to the fear of severe side effects and the required regularly monitoring, see Summary of Product Characteristics (SPC). Thus, we extended the definition of TRS to include patients meeting eligibility criteria for clozapine adapted from the definition of Kane and colleagues and as reflected by 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). Accordingly, 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 identifying redeemed outpatient prescriptions of antipsychotics (ATC codes N05A, excluding N05AN01 (lithium)). See Table A1 in the Supplementary material for a 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 areas, and 3) rural areas, 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 treatment resistance, as defined above, reporting hazard rate ratios (HR) and 95% confidence intervals (CI) from Cox proportional hazards regression analysis. All analyses were adjusted for age and calendar year of first schizophrenia diagnosis, and allowed different baseline hazards for males and females. Additionally, we calculated estimates in a model also adjusted for other sociodemographic 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. Although we found no major violations of the proportional hazards assumption for urbanicity, we did observe that the effect of urbanicity diminished over time and we explored this in a secondary analysis. 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 were two-sided and declared significant at the 5% level. All estimates are accompanied by 95% confidence intervals.

2.6. Sensitivity analyses

We conducted several sensitivity analyses to investigate the robustness of the results. First, we repeated the analyses using clozapine initiation only as a proxy for TRS. Second, to account for the fact that >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 analysis was repeated using a more detailed five-level categorization of the urbanicity exposure (capital, suburb to the capital, provincial city, provincial town, and rural area) as used in a previous study on urbanicity and schizophrenia (Pedersen and Mortensen, 2001b).

Last, all-cause mortality was evaluated across levels of urbanicity.

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

Baseline characteristics (%)	Levels of urbanicity at diagnosis			Total
	Capital area	Provincial areas	Rural areas	
N (%)	4394 (32.9)	5746 (43.0)	3209 (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 disability benefit)[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 (excluding psychotropic drugs mentioned above) 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 Supplementary material.

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%) individuals fulfilled the proxy definition for TRS by meeting at least one of the two criteria for TRS during follow-up, whichever came first; 1210 (9.1%) due to a redemption of clozapine (criterion one) and 1103 (8.3%) due to a hospital admission after at least 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 (Fig. 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.

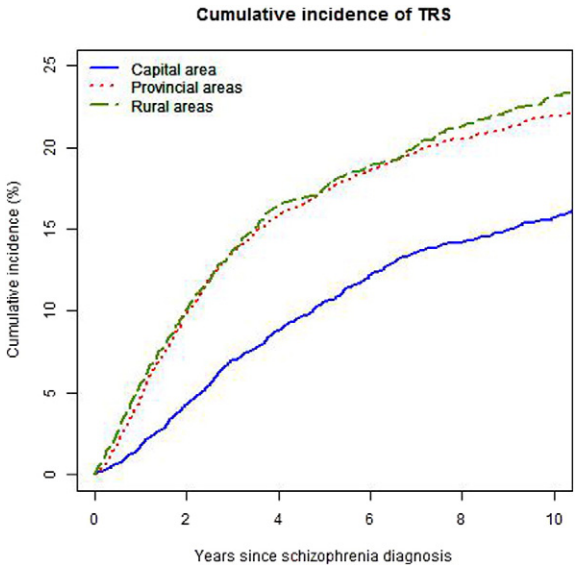

Fig. 1. Cumulative incidence of TRS stratified by level of urbanicity at first diagnosis of schizophrenia. The cumulative incidence measure the probability (or risk) for a person with schizophrenia of meeting TRS criteria according to number of years since first schizophrenia diagnosis.

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).

The cumulative incidence of TRS is shown in Fig. 1. The cumulative incidence measures the probability of meeting the TRS criteria before a given time since the first recorded diagnosis of schizophrenia. Fig. 1 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.

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 (Fig. 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: HR = 1.19 (1.05–1.34) for provincial areas and HR = 1.12 (0.98–1.28) for rural areas.

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

3.1. Sensitivity analyses

When applying the more narrow proxy for TRS (clozapine initiation only), 1424 (10.7%) were defined as treatment resistant during follow-up. Similar results for the association between urbanicity and TRS 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) for provincial areas and HR = 1.17 (0.99–1.38) for rural areas. For urbanicity obtained at different time points between birth and diagnosis of schizophrenia, and for TRS occurring in different years after diagnosis, similar patterns as for the main TRS proxy were seen for clozapine initiation only (Figs. A2 and A3).

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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.

Results of the remaining sensitivity analyses were reported for the main 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).

For the analysis using a more detailed 5-level classification of urbanicity, 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 (Fig. A4).

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. 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. Considering both age at residence and the number of years before first diagnosis of schizophrenia as alternative time points in measuring urbanicity, we found highest urban-rural differences in rates of TRS when urbanicity was measured at time of first schizophrenia diagnosis. 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 we found the effect sizes diminishing with time after diagnosis of schizophrenia. This could to some extent indicate earlier recognition of TRS in rural areas.

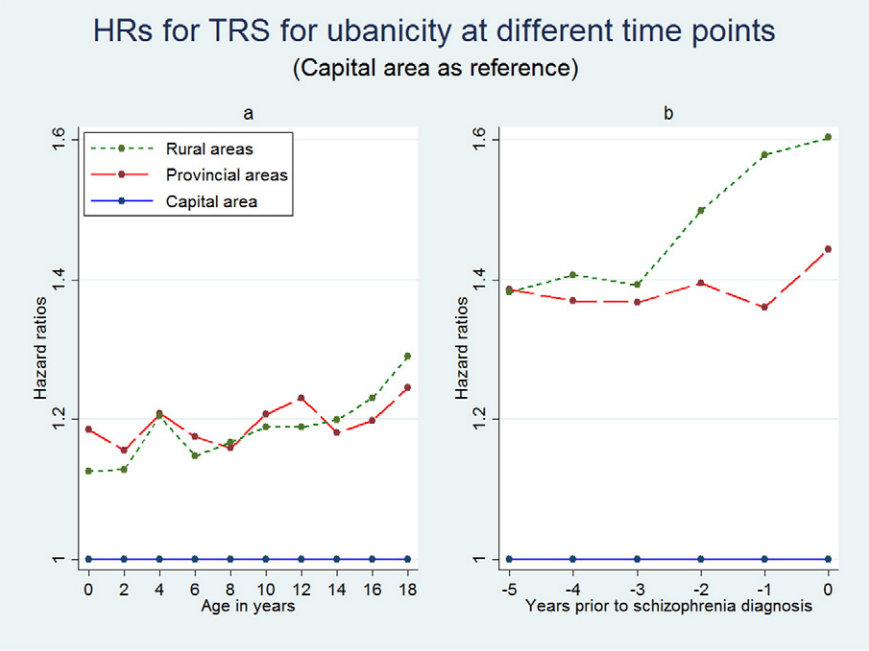

Fig. 2. Hazard ratio estimates for TRS in different models where urbanicity was obtained at different time points. (a) Ages after birth, where the cohort is restricted to individuals born after 1971 to have full information on residence at time of birth. (b) Years prior to first schizophrenia diagnosis.

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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 when restricting to new users of antipsychotic treatment. Moreover, the association between urbanicity at first schizophrenia diagnosis and TRS persisted even when different 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-episode 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). In the present study we found that 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 to some extend be explained by selective migration towards more urban areas due to the development of the disorder or its prodomata (Pedersen, 2015; Freeman, 1994).

Another potential explanation includes the detected excess mortality of schizophrenia in the capital area which may have prevented these individuals from meeting the TRS criteria. 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. In that sense, the applied main TRS proxy may overestimate the true occurrence of treatment resistance. By contrast, the fact that we do not have information on antipsychotic medication during hospitalization implies potential underestimation of the number of monotherapy trials and thereby potential underestimation of treatment-resistant cases defined by our main proxy for TRS. Furthermore, the more narrow proxy of clozapine initiation only is expected to have a positive predictive value close to 100% since almost all patients on clozapine are assumed to meet criteria for treatment resistance, but might also underestimate the true occurrence of TRS, because 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 readmission 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. The fact that we found similar results when restricting to the clozapine initiation only definition indicates 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.

Role of funding source

None.

Contributors

T Wimberley, C Gasse, CB Pedersen, H Støvring, JH MacCabe and HJ Sørensen designed the study and interpreted the results. T Wimberley did the datamanagement, dataanalyses, and wrote the first draft of the manuscript. A Astrup contributed to the datamanagement and dataanalysis. HT Horsdal and PB Mortensen contributed to the interpretation of the results. All authors contributed to and have approved the final manuscript.

Conflict of interest

Henrik Støvring has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers, Astra Zeneca, UCB and AbbVie. Christiane Gasse has previously received unrestricted research grants funded by Eli-Lilly, Lundbeck A/S and Janssen. James H MacCabe is partly funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, UK.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2016.03.021.

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