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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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