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Risk factors of Major Infections in Schizophrenia. A Nationwide Danish Register Study.

Title for running head: Risk factors of Major Infections in Schizophrenia Patients.

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Background: Risk of infections is elevated in patients with schizophrenia. Predicting their occurrence is essential, as infections in this group of patients are associated with prolonged hospital admission and increased mortality. The objective of the current investigation was to identify the potential risk factors of major infection after diagnosis with schizophrenia.

Methods: This national prospective observational cohort study included 7788 people with schizophrenia born in Denmark between 1975-1990. Socio-demographic, psychiatric and health related data were obtained from Danish national registers. The Cox regression model was used for data analyses. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95%CIs) are presented.

Results: The most significant risk factors associated with the development of major infections included young age, female gender, medical comorbidity and substance abuse. A history of treatment with antipsychotics preceding the diagnosis was negatively associated with such morbidity.

Conclusion: This study reports several factors that might increase the risk of infections in individuals with schizophrenia. Early intervention towards infections should be considered in the subpopulation of schizophrenia patients who are at increased risk of infections.

Key words: Schizophrenia, Major Infections, Risk factors, Epidemiology,

1. Introduction

Infections are a frequent occurrence in schizophrenia patients. Recent evidence suggests that not only severe chronic infections like tuberculosis, HIV and hepatitis but also common clinically important infections such as urinary infections and pneumonia are often diagnosed in schizophrenia patients (DE Hert et al. 2011)(Seminog & Goldacre 2013)(Partti et al. 2015)(Davydow et al. 2016). The reason for this association remains unknown. However, several explanations have been proposed, including social disadvantage, limited access to care, poor education, chronic health problems and an unhealthy life style. Another recently suggested explanation is that an increased risk for infections in schizophrenia might be caused by shared genetic-environmental factors (Nielsen et al. 2016a). Infectious diseases are still recognized as the major causes of mortality and morbidity worldwide (GBD 2015 DALYs and HALE Collaborators et al. 2016). Prior research linked early childhood pneumonia with adverse long-term health problems like decreased lung function and chronic obstructive pulmonary disease (Svanes et al. 2010)(Gray et al. 2017)(de Marco et al. 2011). Several other studies demonstrated that infections can lead to cognitive impairment (Leibovici 2013)(Benros et al. 2015). Accelerated physical aging and an elevated risk of death by suicide associated with infections has also been suggested (Gavazzi & Krause 2002)(Lund-Sørensen et al. 2016).

Regarding schizophrenia, an ample body of evidence indicates that infections are generally associated with high frequency of adverse events in this group of patients. First, infections account for leading causes of premature death in schizophrenia (Ribe et al. 2015)(John et al. 2018)(Brown et al. 2010)(Saha et al. 2007).
Secondly, admissions due to infectious diseases in this group of patients are associated with a prolonged and more complicated stay. Unfavorable outcomes including a higher risk of acute respiratory failure, a greater risk of organ failure and increased rates of intensive care unit (ICU) admission was found in hospitalized patients with schizophrenia (Chen et al. 2011)(Shen et al. 2011).

In contrast to the growing evidence linking schizophrenia with infections, there is a dearth of studies investigating risk factors of severe infection following a first diagnosis of schizophrenia. Knowledge of the factors that increase the risk of infection in schizophrenia is essential, as it may aid in identifying patients with a high risk of infection. If reliable risk factors of major infection could be found, this would assist clinicians in identifying patients who would benefit from preventive strategies. In response to a gap in the existing literature, we investigated the impact of a broad range of factors covering important areas i.e., socioeconomic level, familial and health related factors on the risk of infection in schizophrenia patients. The main aim of the study was to find features that are associated with elevated risk of major infections among the first episode of schizophrenia patients. Major infections refer to infections diagnosed and treated in secondary care.

2. Method

2.1 General settings

This study was based on nationwide data, obtained from the Danish population-based registers. The studies data was collected from The Danish Civil Registration System (Pedersen et al. 2006), The Danish National Hospital Register (Andersen et al. 1999), The Danish Psychiatric Central Research Register (PCRR) (Mors et al. 2011), the Danish National Prescription Registry (Wallach Kildemoes et al. 2011), and The Danish Register of Causes of Death (DRCD) (Helweg-Larsen 2011). The study was approved by the Danish Data Protection Agency with the number: 2008-58-0035.

2.2 Study population

The study population consisted of all individuals born in Denmark between 1975-1990 and registered with a diagnosis of schizophrenia (ICD-10; F20, ICD-8; 295) between 1995-2013. In Denmark until 1994, the 8th revision of ICD (ICD-8) was applied; after 1994 the ICD-10 was implemented. For all cases, the date of the first contact with schizophrenia diagnosis was identified and defined as the study start. The study end was defined as contact with major infection, death, migration or study end 31.12.2013. Information about psychiatric diagnoses were derived from the Psychiatric Central Register and were available from 1969.

2.3 Statistical analysis

From the schizophrenia cohort, all patients with inpatient or outpatient contact with the International Classification of Diseases ICD-10 codes for infections (including skin infections, respiratory infections, tuberculosis, HIV, hepatitis, sepsis, urinary infections, gynecological infections, otitis media, other types) were identified (ICD-10 criteria for infections used in the study are listed in an Appendix). Health records were obtained from the National Danish Hospital Register and were available from 1995. To find factors correlated with an increased risk of the infections, we investigated an association between several demographic and clinical features of individuals diagnosed with schizophrenia and the development of an infection during the follow up of the study. Premorbid psychiatric conditions were defined as registered contact with a psychiatric department with a depressive episode (F32 (ICD-10) and 296.0, 292.2, 296.9, 298.0, 300.4 (ICD-8)) or anxiety (F40-F.42 (ICD-10) and (3001, 3004, 3005 (ICD-8)) prior to the date of schizophrenia, this information was obtained from the Danish Psychiatric Central Register. Prescription
drugs affecting the central nervous system (psychopharmacological treatment) were defined as an individual being prescribed antipsychotics, anxiolytics, antidepressants or drugs for insomnia (for ATC-codes used in the study see Appendix). Records of redemption of psychopharmacological treatment for cohort members and their parents were found in the Danish National Prescription Registry and were available from 1995. Somatic premorbid conditions were defined as inpatient or outpatient contact because of the conditions within the Charlson Comorbidity Index before study entry (Charlson et al. 1987). We, however, excluded HIV from somatic premorbid conditions because HIV was a component of our outcome measure (for a detailed description of medical conditions used in the study see an Appendix). The impact of obesity and substance abuse (inclusive alcohol abuse and related conditions) on the outcome with an infection was also assessed as previous studies provided evidence of a positive association between those factors and the risk of an infection (Huttunen & Syrjänen 2013; Falagas & Kompoti 2006; Trevejo-Nunez et al. 2015). ICD-10 codes for somatic premorbid conditions inclusive obesity and substance abuse used in the study are listed in an Appendix). Information about redemption of antibiotics was also available and was obtained for the cohort members from the Danish National Prescription Registry (for ATC-codes used in the study see an Appendix). Education level was defined as the highest completed level of education and grouped by the following stratification adapted to the International standard classification of education ISCED97 into four categories: primary and lower secondary education (9-10 years of education), upper secondary education (10-12 years of education), higher education (13-20 years of education) and missing. Parental income was measured for both mother and father cohort members and sorted into groups: low, middle, high and unknown (for detailed information about income levels see an Appendix). Parental variables were recorded at the end of the observation period while variables of cohort members were recorded up to the study start. By limiting the scope of the study to pre-diagnostic factors, we wanted to find clinical features associated with elevated risk for infection following a first diagnosis of schizophrenia. By choosing infections diagnosed at hospitals, we wanted to minimize information bias related to differences in the help-seeking behavior. Cox proportional hazards modeling using SAS PHREG procedure in the SAS version 9.4 (SAS Institute, Cary, NC) was used to determine characteristics at study entry to first inpatient or outpatient contact with a major infection in the schizophrenia cohort. All statistical tests were two-sided. The results were returned as hazard ratios with 95% confidence intervals and p-values. All risk factors were coded as dummy or categorical variables and analyzed on unadjusted and adjusted levels. The proportional hazard assumption was evaluated by test applying PROC PHREG procedure in SAS and found valid. To identify potential risk factors of major infection a stepwise approach was used using threshold of P<0.05. Additional analyses estimating an association between investigated factors and the risk of recurrence of infection were also performed. Furthermore, the long-term impact of factors on the outcome with infection was assessed. The latter analyses used stepwise approach on P<0.05 level. Multicollinearity was tested by Spearman’s correlation coefficient test for all variables included in the final (adjusted) model. The test showed no correlation between age, gender, somatic comorbidity, substance abuse and redemption of antipsychotics before the diagnosis. Both crude and adjusted analyses were adjusted for the calendar period (stratification). Calendar periods consisted of 4 periods in which individuals were diagnosed with schizophrenia: 1995-1999; 2000-2004; 2005-2009; 2010-2013. Subgroup analyses stratified by age and gender were performed, and adjusted for calendar period, physical illness, substance abuse, and premorbid use of antipsychotics. As previous studies reported positive association between former infection and the risk of infections, all analyses were adjusted for history of hospital contact with infection prior to the study start (stratification) (Melvin et al. 2017); (Abad et al. 2017)(Hamilton et al. 2013).

3. Results:

3.1 Risk factors of major infection in the schizophrenia cohort in crude and adjusted results
During the follow-up time from the study’s entry until death, migration or 31 December 2013 or incidence of major infection, a total of 872 (11.19%) patients developed a major infection. The results are presented in table 1 and table 2. In crude analyses (table 1), several demographic factors, health-related and socio-economic variables were significantly associated with a major infection. Individual risk factors included: younger than 25 years age at the schizophrenia diagnosis, female gender, premorbid psychiatric morbidity with depression, medical comorbidity, and substance abuse. Higher education achievement, on the other hand, showed an inverse association with major infections. Among psychopharmacological drugs, only premorbid treatment with antipsychotic showed a significant inverse association with the risk of major infections in crude analyses. With regards to parental variables, a positive association was found between redemption of psychopharmacological drugs by father and the risk of major infection in offspring. Level of parent’s income did not have any effect on the outcome with major infections in offspring.

The adjusted analysis (table 2) largely reduced the number of risk factors of major infections. Younger age at schizophrenia onset, female gender, somatic comorbidity, and substance abuse was associated with increased the risk of infection while the premorbid psychopharmacological treatment with antipsychotics retained its negative association with the risk of major infections after adjustment (HR=0.71, CI 95% 0.62-0.82). Premorbid psychiatric morbidity in the adjusted model did not confer a greater risk of major infections. The remaining crude variables entered the adjusted hazard regression model did not show a significant effect.

3.2 Risk factors of major infections by age group at schizophrenia diagnosis.

Among patients less than 16 years at schizophrenia onset, 23% developed major infections during the follow-up of the study whereas lower prevalence was found in two remaining strata of age (16-25 years and over 25 years, among which 11% and 11% developed a major infection, respectively). Performed crude and adjusted analyses showed an inverse association between younger age less than 25 years and the risk of major infection. Risk factors by age group are presented in table 3. Several different associative factors with major infections were found in the three strata of age at schizophrenia onset. In the youngest group (under 16 years) only female gender was significant associated with the risk of major infection, whereas female gender, somatic comorbidity, and substance abuse had a significant effect in both age strata: 16-25 and over 25. Redemption of psychopharmacological treatment in form of antipsychotics was associated with a significantly decreased risk of major infection only in the group of patients between 16-25 years.

3.3 Association between age, gender and the risk of major infection

Association between gender and age is presented in table 4. In subgroup analyses stratified by gender we found that in females, significant association with the risk of major infections was found in individuals under 16 but not among individuals aged 16-25 years. In contrast individuals between 16-25 years had an increased risk of major infection in males but not those less than 16 years.

3.4 Frequency of types of major infection by age group.

Distribution of different types of major infections across three age groups at schizophrenia onset is presented in table 5. The data documented differences in the presence of various types of infections across the age strata. The most prevalent infections in the youngest group of schizophrenia patients were skin infections followed by other types of infection, respiratory infections and gastrointestinal infection. The four most prominent infections in the group of patients between 16-25 and the group over 25 years were: skin infections, gastrointestinal infections, respiratory infections and other types of infection. We found no cases of hepatitis, HIV, CNS, or tuberculosis among the youngest group of patients.
3.5 Risk factors of an episode with major infection 1800 days after the diagnosis

To assess the potential long-term impact of investigated candidate factors on the risk with major infection, we further performed analyses for the population at the time of 1800 days following the schizophrenia diagnosis. Among 4415 persons 355 developed an infection. One medical condition (HR=1.76 CI 95% 1.26-2.48) p<0.001 together with female gender ((HR=1.95 (1.58-2.41) p<0.0001) turned out to have a positive association with the risk of major infections in individuals with schizophrenia 1800 days after the diagnosis.

4. Discussion

Risk factors of infections in schizophrenia has not been investigated yet. In this paper, we report possible factors associated with an occurrence of major infections in individuals with a first-time diagnosis of schizophrenia. Our findings demonstrate that young age, female gender, medical comorbidity, and substance abuse before the time of the first diagnosis with schizophrenia might contribute to an increased risk of major infections. Premorbid redemption of antipsychotics seems to have an inverse, significant association with the risk of major infection. Some of our findings on the effect of medical comorbidity or substance abuse follow aggregated knowledge in this field, while the impact of other factors such as age, female gender, and redemption of antipsychotics preceding the diagnosis on the risk with major infection is poorly understood and need further discussion.

4.1 Age at onset of illness and its association with an event with major infection.

The correlation between age and the susceptibility to infections has been assessed in several studies, and it is today well established that children and adolescents are more prone to experience infection. This increased risk of infections in young patients is attributed to both biological and behavioral differences in comparison to adults. Adult patients appear to have better ability to recognize and communicate symptoms of infections compared to younger patients. Similarly, older patients with schizophrenia might be expected to have developed better coping strategies, a greater understanding of their disorder and consequently better adherence to treatment. Differences in clinical features and trajectories of schizophrenia course have been previously documented, concerning the age at schizophrenia onset. General impression presumes that patients with early onset of schizophrenia (onset of illness before age of 18) constitute a more debilitated group of patients (Stentebjerg-Olesen et al. 2016). Thus, one of the possible explanations of the data is that an increased risk of infections attributed to younger age at schizophrenia onset might be related to the younger biological age. However, it could also be related to greater severity of schizophrenia symptoms linked with early schizophrenia onset. Differences related to age at schizophrenia diagnosis were also found with regards to occurrence patterns of different types of major infections. For instance, we found no cases of hepatitis, HIV, or tuberculosis among patients less than 16 years at schizophrenia onset. The course and the result of infection are governed by many complex variables. Thus, this discrepancy in the prevalence of different types of infections across age groups might reflect different pathways by which the result of major infection was determined. Of these, age-related immune status of the host, host population density, lifestyle, and environmental conditions could be considered important determinants. The data documenting an association between age at onset of schizophrenia and infection is scarce; however, available literature supports our finding. The Nielsen study found that time before the age of 17 was associated with almost two folds increased risk of suffering from both conditions: schizophrenia and infection than if the two conditions had occurred independently. The probability of such occurrence declined with the increase in age (Nielsen et al. 2016b).

4.2 Association between gender and risk of major infection

Data from this study demonstrated that increased risk of infections was attributed to the female gender and this association was strongly related to the youngest age. The reasons for these associations may lie in both biological and behavioral differences between genders, but it could also arise from differences in sex associated with schizophrenia. Generally, females appear to onset at a later age compared to males and
tend to have a milder course of the illness (Canuso & Pandina 2007). However, early onset schizophrenia has been correlated with moderate to severe grade of symptoms regardless sex (Ordóñez et al. 2016). Consequently, female diagnosed with schizophrenia at younger age might be affected by more severe grade of symptoms. Thus, the high magnitude of the association between the female gender and risk of major infection in the younger strata could at least partly reflect the greater severity of the schizophrenia in younger females. The increased risk of infections could be mediated by stress or lower function level associated with the stronger severity of symptoms. Immunological aberrations e.g., increased level of IL-6 responsible for inflammatory responses have also been linked to the severity of symptoms in schizophrenia (Müller & Schwarz 2010). Other studies found that abnormal levels of such inflammatory cytokine markers like IL-1Ra and sTNF-R1, could be also correlated with both general disease severity and psychotic features in schizophrenia (Hope et al., 2013).

Whether and to what degree observed differences could be caused by hormonal differences between gender and their interplay with the immune system or are correlated with gender differences in schizophrenia cannot be answered in this study setting and it needs to be assessed in more detail in future studies. In our previous work, we found that female gender was associated with elevated risk of infections in both schizophrenia patients and controls form the general population. However, the association between age and gender have not been evaluated (Pankiewicz-Dulacz et al. 2018). Former literature reported higher risk of sexual transmitted infections in young females when compared to males, although differences in occurrence patterns between all spectrum of infectious diseases between genders in adolescence have not been sufficiently elucidated (Allen et al. 2014).

4.3 Somatic comorbidity and alcohol and substance abuse and risk of major infection

The results support the notion that somatic comorbidity and substance abuse are associated with an increased risk of major infection, which follows previous research. Both physical illness and substance abuse can suppress the immune system, hence increase susceptibility for acquiring infection. Alcohol and substance abuse can be also correlated with the unhealthy life style and by this pathway increase the risk of acquiring infection. The additionally conducted analyses restricted to time 1800 after schizophrenia diagnosis showed a significant effect of somatic comorbidity on the risk of major infection. This finding could imply that physical illness might be considered as long-term predictors for acquiring major infection in schizophrenia.

4.4 Familial and psychosocial factors and their association with an episode with major infection in schizophrenia

Results from this study showed that the risk of major infections was not associated with socioeconomic status indicated by level of the parent’s income. However, additional conducted analyses estimating the risk of recurrent infection showed that among all investigated factors (listed in table 1) only “missing father (father not alive)” was a significant factor of recurrence of major infection with HR=1.67 (1.01-2.75) on a level of p=0.04. The educational attainment was significantly associated with the risk of major infection only in crude analyses. Diminishing of the impact of education in the adjusted analyses might indicate a correlation between the education and other factors. Prior research provides evidence of association between somatic illness and education (Lobo-Escolar et al. 2008).

4.5 Premorbid psychopharmacological treatment and it is association with a risk of an episode with major infection in schizophrenia

Data generated from this study showed that individuals with a history of premorbid treatment with anxiolytics, antidepressants and medication for insomnia did not have an elevated risk of infections in schizophrenia. In contrast, individuals who received a treatment with antipsychotics before the diagnosis had a decreased risk of contracting infection in the age group 16-25 years. This observation is somewhat against the evidence that hypnotics and antipsychotics are associated with an increased risk of some types of infections (Benzodiazepines and related drugs: pneumonia. 2014)(Obiora et al. 2013)(Brandt & Leong 2017)(Nakafero et al. 2016)(Correll et al. 2015). A possible explanation, however, could be that patients receiving
antipsychotic treatment are regularly monitored for side-effects of the medicine inclusive blood test. For instance, the subgroup of patients who receive Clozapine treatment undergo close monitoring of white blood counts. Thus, some of the signs of the infection could be detected earlier compared to those who don’t receive the treatment. This finding could also reflect the possibility that this group of patients is generally more compliant to the treatment. Prior treatment with the antipsychotics could also be associated with a shorter duration of untreated psychosis (DUP), which constitute an important predictor of schizophrenia course. Positive effects of antipsychotic treatment have been documented with regards to better survival rates in schizophrenia patients (Tiihonen et al. 2016). However, a lack of data about prescriptions in the period following the schizophrenia diagnosis could potentially bias the results. Thus, the finding should be interpreted cautiously.

4.6 Strengths and limitation

The main strength of this study is the nationwide schizophrenia cohort and their follow-up based on register data which includes records of all residents. Linkage via a unique personal number to different registers gave us the possibility to adjust for a vast number of factors covering different life categories and allowed us to obtain more exact estimates on an individual level. Data about prescriptions, schizophrenia diagnosis, infections, and Charlson comorbid conditions have high validity and completeness; however, data regarding obesity might be underestimated (Rasmussen et al. 2016)(Schmidt et al. 2015)(Uggerby et al. 2013)(Thygesen et al. 2011). The prevalence of obesity estimated in our study was 2.49% which is lower than reported prevalence in a similar sample from the recent study 3.8%-7.5% (Horsdal et al. 2017). We chose to explore many risk factors to create the clinical profile of individuals with the first-time record with schizophrenia who might be at increased risk of developing hospital required infection. Past studies provide an evidence that first four to eight years following schizophrenia diagnosis are associated with the high risk of psychotic relapse and a greater symptoms severity; hence this time could be expected to be more sensitive for acquiring infections. Therefore, the scope of our investigation was limited to the time following the first schizophrenia diagnosis. However, the latter could be also considered as a limitation of the study, as the data cannot be generalized to all patients with schizophrenia across different age groups and time of the schizophrenia course. Furthermore, the outcome with infection is a result of a complex interplay between several factors where some of them might be related with each other. Therefore, the association of potential factors with the outcome might be difficult to assess even with multivariate analysis. Multivariate analyses are additionally associated with the risk of positive false results—the type I error. We tried to reduce the chance of the error by choosing factors related with the risk of infection based on prior literature, by testing covariates for correlation, repeating the analyses using different threshold which posed similar results. Another disadvantage of the study is attributed to administrative data, such as Danish health registers, where there is the paucity of information on life-style factors inclusive smoking, physical activity and health behavior in general. Particularly, a lack of data reflecting the global function of patients is a main disadvantage of this study. The other important limitation of the study design is attributed to the date of the onset of schizophrenia. In our study, we assumed that the first registered inpatient or outpatient contact with a diagnosis of schizophrenia reflects the real time of schizophrenia onset. Thus, the possibility of bias caused by unregistered diagnosis before this date exists. However, the distribution of the age at the registered diagnosis reflects distribution of age at schizophrenia onset described in the literature.

4.7 Conclusion and Implication. In summary, while there is a growing body of evidence linking schizophrenia with elevated risk of infection, features predisposing to such an association are still poorly understood. This study attempted to investigate several factors that might be associated with an increased risk of major infections in individuals recently diagnosed with schizophrenia. Among these, factors related to physical illness were positively associated with the risk of developing major infection. Individuals with a history of a treatment with antipsychotics had a decreased risk of development of major infection.
Additionally, we found the modifying effect of age and gender. This finding emphasizes the heterogeneity of the schizophrenia disorder also concerning the risk of infections. A better understanding of the mechanisms that underlie this heterogeneity needs further assessment, and it is important for better clinical care and optimal interventions for the individual patients.

Contributors

All authors contributed to the design of the study. M. Pankiewicz-Dulacz did the literature searches and the analyses with help of Erik Christiansen, cand.scient.o econ, Ph.d. All authors contributed to and have approved the final manuscript.

Acknowledgments

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The funders had no role in the study design, decision to publish, or preparation of the manuscript.

Ethical considerations

Approval from the ethics committee was not needed as we only worked with anonymous data from registers.

Declaration of interest

None

Table 1. Hazard Rates of major infections after first psychiatric record with schizophrenia diagnosis among birth cohort 1975-1990. Crude levels for all.

<table>
<thead>
<tr>
<th>Age at study entry</th>
<th>N-number of persons in strata</th>
<th>%</th>
<th>Hazard Rate HR</th>
<th>Confidence Intervals 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16</td>
<td>130</td>
<td>1.67%</td>
<td>1.74 **</td>
<td>(1.16-2.60)</td>
</tr>
<tr>
<td>16-25</td>
<td>530</td>
<td>68.07 %</td>
<td>1.30 **</td>
<td>(1.08-1.55)</td>
</tr>
<tr>
<td>&gt;25</td>
<td>2357</td>
<td>30.26%</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Gender (Female)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4730</td>
<td>60.73%</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary education</td>
<td>1899</td>
<td>24.38%</td>
<td>0.82 ***</td>
<td>(0.69-0.98)</td>
</tr>
<tr>
<td>Higher education</td>
<td>194</td>
<td>2.49%</td>
<td>0.37 ***</td>
<td>(0.15-0.89)</td>
</tr>
<tr>
<td>Missing</td>
<td>351</td>
<td>4.51%</td>
<td>1.04</td>
<td>(0.78-1.38)</td>
</tr>
<tr>
<td>Primary education</td>
<td>5344</td>
<td>68.62%</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Somatic comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One Charlson medical condition</td>
<td>812</td>
<td>10.43%</td>
<td>1.57 *</td>
<td>(1.28-1.91)</td>
</tr>
<tr>
<td>Two Charlson medical conditions</td>
<td>63</td>
<td>0.81%</td>
<td>3.70 *</td>
<td>(2.33-5.88)</td>
</tr>
<tr>
<td>Three Charlson medical conditions</td>
<td>12</td>
<td>0.15%</td>
<td>2.22</td>
<td>(0.55-8.93)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----</td>
<td>-------</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>No underlying disease</td>
<td>6901</td>
<td>reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance and alcohol abuse and related conditions (yes)</td>
<td>1340</td>
<td>17.21%</td>
<td>1.36**</td>
<td>(1.14-2.62)</td>
</tr>
<tr>
<td>Obesity (yes)</td>
<td>194</td>
<td>2.49%</td>
<td>1.32</td>
<td>(0.87-2.01)</td>
</tr>
<tr>
<td>Redemption of antibiotics (yes)</td>
<td>6904</td>
<td>1.09</td>
<td>(0.88-1.35)</td>
<td></td>
</tr>
</tbody>
</table>

### Premorbid psychiatric morbidity

| Anxiety (yes) | 1283 | 16.47% | 1.04 | (0.86-1.25) |
| Depression (yes) | 2384 | 30.61% | 1.20 *** | (1.04-1.39) |

### Redemption of psychopharmacological treatment before diagnosis

| Antipsychotics (yes) | 5197 | 66.73% | 0.75 * | (0.65-0.86) |
| Antidepressants (yes) | 4859 | 62.39% | 1.02 | (0.88-1.17) |
| Anxiolytics (yes)     | 3236 | 41.55% | 0.98 | (0.85-1.12) |
| Medication for insomnia (yes) | 2577 | 33.09% | 0.96 | (0.84-1.11) |

### Marital status

| Married | 559 | 7.18% | 0.87 | (0.66-1.14) |
| Partnership/ divorced | 16 | 0.21% | 1.73 | (0.55-5.39) |
| Never married | 7213 | 92.62% | reference |

### Parental risk factors - Mother

| Redemption of psychopharmacological treatment (yes) | 5345 | 68.63% | 1.14 | (0.98-1.32) |

#### Level of income

| Middle | 4720 | 60.60% | 0.97 | (0.83-1.13) |
| High   | 1072 | 13.76% | 0.91 | (0.73-1.15) |
| Missing (not alive) | 81 | 1.04% | 0.80 | (0.39-1.62) |
| Low    | 1915 | 24.58% | reference |

#### Level of income - Father

| Level of income | 3944 | 50.64% | 1.06 *** | (1.01-1.23) |
| Middle         | 3491 | 44.82% | 0.98 | (0.83-1.17) |
| High           | 2314 | 29.71% | 0.98 | (0.81-1.18) |
| Missing (not alive or not known) | 264 | 3.38% | 1.09 | (0.76-1.57) |
| low            | 1719 | 22.07% | reference |

*P<0.0001
** P <0.01
*** P<0.05

Adjusted for calendar period (stratification) and for prior hospital contact due to infection (stratification)

---

**Table 2.** Hazard Rates of major infections after first psychiatric record with schizophrenia diagnosis among birth cohort 1975-1990. Adjusted levels for all.

<table>
<thead>
<tr>
<th>Age at study entry</th>
<th>N-persons in strata</th>
<th>Adjusted Hazard Rate</th>
<th>Confidence Intervals 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16</td>
<td>130</td>
<td>1.59 **</td>
<td>(1.06-2.39)</td>
</tr>
<tr>
<td>16-25</td>
<td>5301</td>
<td>1.27 **</td>
<td>(1.05-1.52)</td>
</tr>
</tbody>
</table>

---
<table>
<thead>
<tr>
<th>&gt;25</th>
<th>2357</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td>3058</td>
<td>1.83 * (1.59-2.09)</td>
</tr>
<tr>
<td>Male</td>
<td>4730</td>
<td>reference</td>
</tr>
</tbody>
</table>

Somatic comorbidity

- One Charlson medical condition | 812 | 1.53 * (1.28-1.91) |
- Two Charlson medical conditions | 63 | 3.42 * (2.33-5.88) |
- Three Charlson medical conditions | 12 | 2.55 (0.55-8.93) |
- No underlying disease | 6901 | reference |

Substance and alcohol abuse and related conditions (yes) | 1340 | 1.48* (1.14-2.62) |

Redemption of psychopharmacological treatment before diagnosis

- Antipsychotics (yes) | 5197 | 0.71 * (0.62-0.82) |

*P<0.0001
** P<0.05

Adjusted for calendar period (stratification), prior hospital contact due to infection (stratification) and remaining covariates from the table.

Notes. All estimates adjusted for calendar period, prior hospital contact due to infection, and remaining covariates from the table.

Table 3. Hazard Ratio of major infections after first record with schizophrenia diagnosis in birth cohort 1975-1990, by age. Adjusted estimates for all.

<table>
<thead>
<tr>
<th></th>
<th>Number of persons in strata</th>
<th>Age &lt; 16 N=130</th>
<th>Number of persons in strata</th>
<th>Age 16-25 N=5301</th>
<th>Number of persons in strata</th>
<th>Age &gt; 25 N=2357</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>CI 95%</td>
<td>HR</td>
<td>CI 95%</td>
<td>HR</td>
<td>CI 95%</td>
</tr>
</tbody>
</table>

Gender (Female)

- Male | 60 | 4.5** 1.79-11.30 |
- Female | 70 | reference |

Somatic comorbidity

- One Charlson medical condition | 3120 | 1.84* 1.57-2.14 |
- Two Charlson medical conditions | 807 | 1.50** 1.08-2.07 |
- Three Charlson medical conditions | 1550 | reference |
- No underlying disease | 2181 | reference |
All estimates adjusted for calendar period, prior hospital contact due to infection, gender, somatic comorbidity, substance abuse, redemption of antipsychotics before the diagnosis.

Table 4. Hazard Ratio of major infections after first record with schizophrenia diagnosis in birth cohort 1975-1990, divided by gender.

| One Charlson comorbidity | 13 | 2.66 | 0.93-7.63 | 494 | 1.48** | 1.17-1.88 | 305 | 1.58** | 1.06-2.35 |
| Two Charlson comorbidities | - | - | - | 31 | 3.09** | 1.63-5.84 | 32 | 4.02* | 1.99-8.12 |
| Three Charlson comorbidities | - | - | - | 4 | 2.14 | 0.29-15.38 | 8 | 2.88 | 0.39-21.13 |
| No underlying disease | 117 | reference | 16.88 | 764 | reference | 1.39** | 1.13-1.72 | 573 | 1.61** | 1.14-2.27 |
| Substance and alcohol abuse (yes) | 3 | 2.85 | 0.48-16.88 | 3511 | 0.67* | 0.57-0.79 | 1610 | 0.97 | 0.86-1.23 |

Redemption of psychopharmacological treatment before the diagnosis

| Antipsychotics (yes) | 76 | 0.95 | 0.42-2.13 | 76 | 0.95 | 0.42-2.13 | 76 | 0.95 | 0.42-2.13 |

"P<0.0001
** P<0.05
Adjusted for calendar period (stratification) and for prior hospital contact due to infection (stratification)

All estimates adjusted for calendar period, prior hospital contact due to infection, gender, somatic comorbidity, substance abuse, redemption of antipsychotics before the diagnosis.

All estimates adjusted for calendar period, prior hospital contact due to infection, somatic comorbidity, substance abuse and of redemption of antipsychotics before the diagnosis.

Table 4. Hazard Ratio of major infections after first record with schizophrenia diagnosis in birth cohort 1975-1990, divided by gender.

<table>
<thead>
<tr>
<th>Age at illness onset</th>
<th>Females N=3058</th>
<th>Males N=4730</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16</td>
<td>1.82 ** 1.12-2.95</td>
<td>1.02 0.44-2.38</td>
</tr>
<tr>
<td>16-25</td>
<td>1.22 0.93-1.59</td>
<td>1.34 ** 1.04-1.73</td>
</tr>
<tr>
<td>&gt;25</td>
<td>reference</td>
<td>reference</td>
</tr>
</tbody>
</table>

**P<0.05

All estimates adjusted for calendar period, prior hospital contact due to infection, somatic comorbidity, substance abuse and of redemption of antipsychotics before the diagnosis.

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Table 5. Distribution of major infections during the follow-up of the study, by age categories: number and percentage (%) of patients in the schizophrenia experiencing major infection after the schizophrenia diagnosis.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Age &lt;16 years</th>
<th>Age 16-25 years</th>
<th>Age &gt; 25 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases (%)</td>
<td>Number of cases (%)</td>
<td>Number of cases (%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (0.77%)</td>
<td>37 (0.69%)</td>
<td>18 (1.5%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0</td>
<td>64 (1.2%)</td>
<td>48 (2.03%)</td>
</tr>
<tr>
<td>Gastrointestinal infections</td>
<td>10 (7.7%)</td>
<td>485 (9.14%)</td>
<td>242 (10.26%)</td>
</tr>
<tr>
<td>Skin infections</td>
<td>18 (13.8%)</td>
<td>606 (11.43%)</td>
<td>285 (12.09%)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>13 (10%)</td>
<td>479 (9.42%)</td>
<td>222 (9.42%)</td>
</tr>
<tr>
<td>Genital infections</td>
<td>4 (3%)</td>
<td>167 (3.15%)</td>
<td>66 (2.8%)</td>
</tr>
<tr>
<td>Urogenital infections</td>
<td>9 (6.92%)</td>
<td>237 (4.47%)</td>
<td>105 (4.45%)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>9 (6.92%)</td>
<td>115 (2.17%)</td>
<td>41 (1.74%)</td>
</tr>
<tr>
<td>CNS</td>
<td>0</td>
<td>27 (0.50%)</td>
<td>15 (0.63%)</td>
</tr>
<tr>
<td>HIV</td>
<td>0</td>
<td>4 (0.075%)</td>
<td>8 (0.34%)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>6 (0.11%)</td>
<td>5 (0.21%)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (12.3%)</td>
<td>456 (8.60%)</td>
<td>190 (8.06%)</td>
</tr>
</tbody>
</table>

Literature


Schizophrenia bulletin 37, 1088–94.


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## Appendix

### Infections assessment:
- Sepsis (ICD-10: A40, A41)
- Hepatitis (ICD-10: B15-B19)
- Gastro-intestinal infections (ICD -10: A00-A09, K35)
- Skin infections (ICD-10: L00-L08, B00-B09, A 46)
- Respiratory infections (ICD-10: J00-J18)
- Urological infections (ICD-10: N00, N10, N300, N390)
- Otitis media (ICD-10: H65-H67)
- HIV (ICD-10:B20-B24)
- Tuberculosis (ICD-10: A15-A19)
- Other type of infection (the remaining infections within the general chapters ICD-10: A, B or M0).

### Comorbidity component:
- Myocardial Infarction (ICD-10: I21;I22;I23)
- Congestive Heart Failure (ICD-10:I50;I11.0;I13.0; I13.2)
- Peripheral Vascular Disease (ICD-10: I70;I72;I73;I74;I77)
- Cerebrovascular Disease (ICD-10: I60-I69;G45;G46)
- Dementia (ICD-10:F00-F03;F05.1;F30)
- Chronic pulmonary diseases (ICD-10:J40-J47;J60-J67;J68.4;J70.1;J70.3; J84.1; J92.0; J96.1;J98.2; J98.3)
- Connective Tissue Disease (ICD-10: M05;M06;M08;M09;M30;M31;M32;M33;M34;M35;M36;D86)
- Peptic Ulcer Disease (ICD-10: K22.1;K25-K28)
- Diabetes Mellitus (ICD-10: E10-E11)
- Moderate to Severe Chronic Kidney Disease (ICD-10: I12; I13; N00-N05,N07;N11; N14;N17-N19;Q61)
- Hemiplegia (ICD-10: G81;G82)
- Cancer (ICD-10: C00-C96)
- Liver Disease (ICD-10)
- Obesity (ICD-10: E65; E66)
- Substance and Alcohol abuse and alcohol related diseases (ICD-10: F10- F19;G31.2;G72.1; I42.6;K29.2; R78.0;T51;Z72.1)
- Inflammatory bowel syndrome (ICD-10; K50-K52)
- Pancreatitis (ICD-10; K85; K86.0;K86.1)

### Psychopharmacological treatment
- Antipsychotics: N05A
- Antidepressants: N06A
- Anxiolytics: N05BA, N05CD, N03AX16, N03AE01, N05BB, N05BE
- Drugs for insomnia: N05CF01, N05CF02, N05CF03, N05CH01

### Antibiotics
- J01BA (amfenicols)
- J01CE (B-laktamase sensitive penicillins)
- J01CF (B-laktamase resistant penicillins)
- J01CG Beta-lactamase inhibitors
- J01DE (4 generations cephalosporins)
- J01DF (monobactams)
- J01EA (trimethoprim)
- J01EB (short acting sulfonamides)
- J01EC Intermediate-acting sulfonamides
- J01ED (Long-acting sulfonamides)
- J01FA (macrolides)
- J01FF (lincosamides)
- J01XA (glycopeptides antibacterias)
- J01XC (steroid antibacterias)
- J01XD (imidazole derivatives)
(nitrofuran derivatives), J01XX (other), J01XX05, J01XX09J01A, J01 AA (tetracyclines), J01CA (penicillins with extended spectrum), J01CR (combinations of penicillins, including β-lactamase inhibition), J01DB (1 generation cephalosporins), J01DC (2 generation cephalosporins), J01DD (3 generation cephalosporins), J01DH (carbapenems), J01DI (Other cephalosporins and penems), J01EE (combination of sulfonamide and trimethoprim, including derivatives), J01GA (Streptomycins), J01GB (other aminoglycosides), J01MA (fluoroquinolones), J01MB (other quinolones), J01XB (polymyxins), A01AB09 (Miconazol), A07AA02 (Nystatin), J01XX08, A07AA09, J01XA01 (Vancomycin), J01XA02 (Teicoplanin), Fusidin, X01, J01XD01, P01AB01 (Metronidazol), J01XX08 (Oxazolidinone), J01XX09 (Daptomycin), J04AB (Rifamycyner), J01RA (Combinations of antibacterials), J01, others, P01B, P02D, J02AA01, J02AB, J02CA, J02AC, J02AX01, J01CE, J01CF, J01XA, J01CA, J01CR, J01M, J01XD01, P01AB01, J01DB, J01DC, J01DD, J01DH, J01XX08, J01EA, J01EB, J01FA, J01XC, J01XE, J01AA, J01EE, J01FF, J01XX05, J01BA

<table>
<thead>
<tr>
<th>Income</th>
<th>Law &lt;24 444 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Middle: 24 444 – 66 105 USD</td>
</tr>
<tr>
<td></td>
<td>High: &gt; 66 105 USD</td>
</tr>
<tr>
<td></td>
<td>Unknown: all missing</td>
</tr>
</tbody>
</table>
The authors have no competing interest to report
Highlights

- Factors associated with serious infections in schizophrenia has not been investigated yet.
- Physical illness and substance abuse are associated with elevated risk of major infection in schizophrenia.
- Age at schizophrenia onset and gender might have an influence on the risk of major infection.
- Premorbid treatment with antipsychotics before the diagnosis was negatively associated with the risk of major infection in schizophrenia.