Journal of Psychiatric Research 114 (2019) 105–112

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Risk and associated factors for a future schizophrenia diagnosis after an index diagnosis of unspecified psychotic disorder: A population-based study

Jennifer M. Hensel[a,*], Mariette J. Chartier[b], Okechukwu Ekuma[b], Leonard MacWilliam[b], Natalie Mota[c], Richard O. Tachere[a,1], Chelsey McDougall[b], James M. Bolton[a,b,d]

[a] Department of Psychiatry, University of Manitoba, 771 Bannatyne Ave, Winnipeg, Manitoba, R3E 3N4, Canada
[b] Manitoba Centre for Health Policy, Department of Community Health Sciences, University of Manitoba, 408 - 727 McDermot Ave, Winnipeg, Manitoba, R3E 3P5, Canada
[c] Department of Clinical Health Psychology, University of Manitoba, 771 Bannatyne Ave, Winnipeg, Manitoba, R3E 3N4, Canada
[d] Department of Community Health Sciences, University of Manitoba, S113, 750 Bannatyne Avenue, Winnipeg, Manitoba, R3E 0W3, Canada

ARTICLE INFO

Keywords:
Acute and transient psychotic disorder
Administrative data
Classification tree

ABSTRACT

A significant minority of unspecified psychosis presentations progress to schizophrenia. Clinical risk factors can inform targeted referral to specialized treatment programs, but few population studies have examined this. In this study, we used health administrative data for a population-based cohort from Manitoba, Canada to characterize the risk and identify vulnerable subgroups for a future diagnosis of schizophrenia after a diagnosis of unspecified psychotic disorder. Individuals aged 13–60 years with an inpatient or outpatient diagnosis of unspecified psychotic disorder between April 1, 2007 and March 31, 2012, and without any prior diagnosis of schizophrenia or related disorder, were identified (N = 3, 289). The primary outcome was a diagnosis of schizophrenia recorded after the index diagnosis of unspecified psychotic disorder and before March 31, 2015. Adjusted hazard ratios were computed controlling for age, sex, urbanicity, income, prior diagnosis of unspecified psychotic disorder, provider making the diagnosis, prior 12-month psychiatric hospitalization, and prior 12-month diagnoses of mood, anxiety, substance use, or personality disorders, and substance-induced psychosis. A classification tree identified vulnerable subgroups. The cumulative risk of a future diagnosis of schizophrenia was 26% during the follow-up period (mean 4.5 years), with a mean time to diagnosis of 2.0 years. The most vulnerable subgroup was diagnosed by a psychiatrist, younger than 27 years, without a mood or anxiety disorder, male, and residing in a low-income neighborhood; the rate of a subsequent schizophrenia diagnosis was 61.2%. These results support that identification of specific sociodemographic and clinical factors can help clinicians counsel and intervene with those at highest risk.

1. Introduction

The conceptualization and identification of what constitutes a clinical presentation of early psychosis at high risk for progression to a primary psychotic disorder, including schizophrenia, is evolving (Gaebel et al., 2012; Fusar-Poli et al., 2013; Cannon et al., 2016). Current iterations of the International Classification of Diseases, 10th revision (ICD-10) and the Diagnostic and Statistical Manual, 5th edition (DSM-5) contain several diagnoses for clinicians to consider when classifying psychosis. Where a presentation is not clearly consistent with time and/or symptom criteria for schizophrenia spectrum disorders, delusional disorder, affective psychosis or substance/medical illness-related psychosis, clinicians using the ICD-10 may diagnose acute and transient psychotic disorder (ATPD) or non-organic psychosis (World Health Organization, 1992), while those using the DSM-5 would likely diagnose unspecified schizophrenia spectrum and other psychotic disorder (hereafter referred to as unspecified psychotic disorder; previously psychotic disorder not otherwise specified (NOS) in earlier versions of the DSM) (American Psychiatric Association, 2013). Concordance between these diagnostic categories is high, although the 3-month time criterion for ATPD may be more inclusive than what is captured with the DSM category (Pillmann et al., 2002).

Identification of which individuals presenting with unspecified or transient psychosis will go on to develop schizophrenia has been a

* Corresponding author.. Psychealth, 771 Bannatyne Ave, Winnipeg, Manitoba, R3E 3N4, Canada.
E-mail address: jhensel@hsc.mb.ca (J.M. Hensel).
[1] Present address:Department of Psychiatry & Behavioural Neurosciences St. Joseph's Healthcare Hamilton, West 5th Campus Administration - B3, 100 West 5th Hamilton, Ontario, Canada L8N 3K7.

https://doi.org/10.1016/j.jpsychires.2019.04.019
Received 17 December 2018; Received in revised form 16 April 2019; Accepted 18 April 2019

particular focus of study given the prognostic significance, including increased mortality, health care and social needs, and the corresponding opportunities for early intervention (Fusar-Poli et al., 2013, 2017a). A recent meta-analysis of articles reporting on diagnostic stability after a first diagnosis of psychosis (Fusar-Poli et al., 2016), concluded that, on average, diagnosis changed from ATPD or brief psychotic disorder to schizophrenia 21% of the time, and psychotic disorder NOS to schizophrenia 30% of the time. Between 30 and 60% of patients retained the same diagnoses out to an average of 4.5 years of follow-up, with conversion to an affective disorder occurring about 10% of the time. Among the included studies, however, only two used population-level data from Scotland and Denmark (Castagnini and Foldager, 2014; Queirazza et al., 2014), the former accessing hospitalization records only, and the second using a National registry that exclusively captures psychiatric department contacts (Mors et al., 2011). Another recently published population study also used secondary mental health care data from the National Health Service Trust in the United Kingdom in a validation study against findings from the Danish cohort (Rutigliano et al., 2018). The remainder of studies on this topic have relied on smaller samples recruited from inpatient units or specialized first episode psychosis programs, which represent populations already at a higher risk (Fusar-Poli et al., 2012; Cannon et al., 2016), and which may be more prone to loss to follow-up. A range of sociodemographic and clinical risk factors have been examined in relation to any diagnostic change over time, with no clear moderating effect of age, sex, baseline functioning, or substance use found in meta-analysis (Fusar-Poli et al., 2016), although some studies have identified younger age and male sex as associated with progression specificially to schizophrenia (Fusar-Poli et al., 2017b; Queirazza et al., 2014). A number of environmental factors, including parental factors and ethnicity are positively associated with onset of schizophrenia in at risk populations (Fusar-Poli et al., 2017a).

A recent review on the topic of first episode psychosis suggests that the majority of high-risk individuals are not connected to appropriate services for monitoring and intervention (Fusar-Poli et al., 2017a), despite emerging evidence that early intervention can affect the trajectory of the illness (Breitborde et al., 2015; Malla et al., 2017; Anderson et al., 2018a). Clinical risk calculators have been developed by Cannon et al. (2016) in individuals showing baseline high risk or prodromal features, and Fusar-Poli et al. (2017b) for individuals presenting to secondary mental health settings with baseline diagnoses of non-organic and non-psychotic disorders. The applicability of these tools is limited, however, by the criteria used to derive them. For example, Cannon et al.'s tool relies on a positive screen on the Structured Interview for Psychosis Risk Syndromes (Cannon et al., 2016), and Fusar-Poli et al.'s tool requires an ICD-10 diagnosis made in a secondary mental health setting (Fusar-Poli et al., 2017b). The former is largely restricted to research settings and the latter is not as applicable in North America where clinicians are trained to use the DSM, or in non-specialized clinical settings such as primary care. Of note, a longitudinal study of a clinical sample in the United Kingdom demonstrated some variability in diagnostic stability and predictors of change when using respective versions of the ICD versus the DSM (Heslin et al., 2015). Moreover, to the best of our knowledge, there hasn't yet been a published study using population-level data in North America or across all healthcare settings.

This population-based study examines the rate of and time to a diagnosis of schizophrenia after an index diagnosis of unspecified psychotic disorder made in outpatient or inpatient settings by psychiatrists and other providers. Sociodemographic and clinical factors including the presence of pre-morbid psychiatric diagnoses are evaluated as moderators of that risk, with a classification tree providing a clinical assessment algorithm to help identify high-risk individuals.

2. Material and methods

2.1. Data sources

The data in this study were obtained from the Manitoba Population Research Data Repository at the Manitoba Centre for Health Policy, an affiliate of the University of Manitoba in Manitoba, Canada (Jutte et al., 2011) under Health Information Privacy Committee (HIPC) Project Number 2015/2016-65. Datasets for this study included medical claims, hospitalizations, health registry, vital statistics and area-level census data from Statistics Canada. These databases contain individual-level administrative data for all residents of Manitoba excluding a small number of military personnel, RCMP, and prison inmates (Roos et al., 2005). De-identified data are linked by an encrypted personal health information number with > 95% linkage accuracy (Roos et al., 2005). Sociodemographic characteristics were extracted from the population health registry. Diagnoses were extracted from outpatient medical claims and hospitalization records for admitted individuals. Outpatient claims also capture diagnoses generated in emergency department visits that involve a specialist consultation. In Canada, clinicians are trained to use the DSM to diagnose mental disorders, which is subsequently captured in administrative data for outpatient diagnoses using the ICD, 9th revision, Clinical Modification (ICD-9-CM) system (truncated to 3 digits). Inpatient diagnoses are recorded in health administrative databases by trained coders using the complete ICD-10-Canada (ICD-10-CA) system. See Appendix A for details of data sources and the codes used to define diagnostic categories.

2.2. Participants

The cohort consisted of all individuals between the ages of 13 and 60 with a diagnosis of unspecified psychotic disorder received during a hospitalization or outpatient visit between April 1, 2007 and March 31, 2012 (the observation period). The term 'unspecified psychotic disorder' reflects the DSM-IV (psychotic disorder NOS) and DSM-5 (unspecified schizophrenia spectrum and other psychotic disorder) language used by practitioners. Unspecified psychotic disorder was defined as an ICD-9-CM code of 298 in an outpatient medical claim or any inpatient ICD-10-CA codes of F23, F28 or F29. These definitions were chosen based on prior literature and frequency of code use in our administrative data files (see Appendix A). The age range was based on previous literature and data distribution for unspecified psychosis and first schizophrenia diagnoses. We capped the age range at 60 to minimize cases of very late onset schizophrenia (> age 65) which likely represent a different pathophysiology (Folsom et al., 2006). In addition, to focus on individuals who did not have a pre-existing major psychotic disorder, an 8-year lookback period from the index diagnosis was examined for each participant to identify any previous diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder. Individuals who had a prior diagnosis of unspecified psychotic disorder during the lookback period were not excluded, with the first diagnosis identified during the observation period taken as the index diagnosis.

2.3. Sociodemographic characteristics and prior psychiatric diagnoses

Sociodemographic and clinical factors for the study were chosen based on the published literature, as well as ability to define them in the available data. For all individuals in the cohort, we extracted age, sex, urbanicity, and area-level income. Urbanicity was defined as living in a city with population > 60,000. Area level income is a measure of household income in each Manitoba dissemination area which is defined based on geography and population density. For the study, area level income was divided into quintiles and then categorized as lower income (grouping the two lowest income quintiles) and higher income (grouping the three highest). The provider making the index diagnosis of unspecified psychosis was categorized as a psychiatrist or other

(other primary care or specialist physician or nurse practitioner). We extracted whether or not the individual had a prior 12-month psychiatric hospitalization (including being hospitalized at the time of the index diagnosis). We also extracted inpatient or outpatient diagnoses of substance use disorders, mood or anxiety disorders, personality disorders, and substance-induced psychosis made in the 12 months prior to the index diagnosis, as well as any prior unspecified psychotic disorder.

2.4. Primary outcome

The primary outcome was a diagnosis of schizophrenia as an inpatient or outpatient after the index diagnosis of unspecified psychotic disorder. Use of administrative data to define schizophrenia is accurate (Kurdyak et al., 2015), and comparison of algorithms supports a last diagnosis approach (Sara et al., 2014). The diagnosis, once made, is highly stable over time (Fusar-Poli et al., 2016). For this cohort, an additional 3-year follow-up period was added after the observation period, extending the follow-up period until March 31, 2015. Because individuals may have entered the cohort at any time in the 5 years of observation, individual follow-up periods ranged from 3 to 8 years.

2.5. Data analysis

Baseline sociodemographic characteristics and prior 12-month psychiatric diagnoses were compared between those who did and did not receive a diagnosis of schizophrenia with independent t-tests and chi-squared tests. Time to, and factors associated with a diagnosis converting to schizophrenia during the follow-up period were examined with Cox proportional hazard ratios, adjusted for all study variables including sociodemographics, provider making the diagnosis, prior hospitalization, and prior 12-month psychiatric diagnoses. We conducted a classification tree analysis to identify subpopulations of our study cohort that are most at risk of developing schizophrenia after an unspecified psychotic disorder diagnosis. Classification tree analysis is a non-parametric recursive partitioning data mining approach used in identifying mutually exclusive and exhaustive subgroups of a study population when the response (target) variable is binary (Lemon et al., 2003). This method is particularly helpful in assessing and interpreting higher order interaction relationships among dependent variables and also in identifying vulnerable sub-groups that would otherwise be difficult to identify using traditional regression methods such as Cox proportional hazards. Covariates used in the classification tree were the same as those used in the survival analysis. Tests of proportionality assumptions were done using Schoenfeld's residuals and covariates interaction with log of time. SAS version 9.4 and SAS Enterprise Miner 13.2 were used for all statistical analyses.

3. Results

From April 1, 2007 and March 31, 2012, 4889 individuals had a diagnosis of unspecified psychotic disorder in their health administrative data. Of these, 1600 (32.7%) had a previous diagnosis of a primary psychotic disorder in the 8 years preceding the unspecified psychotic disorder diagnosis and were excluded, leaving 3289 individuals in the cohort (Fig. 1). This represented 0.41% of the eligible population of Manitoba age 13–60 (N = 802,047). The characteristics of the cohort are summarized in Table 1. Individuals with unspecified psychotic disorder were more often male (n = 1,746, 53.1%), and living in urban areas (n = 2202 66.9%). A higher proportion of individuals were living in low income areas (n = 1,817, 55.2%). Diagnoses of unspecified psychotic disorders were made 46.3% (n = 1522) of the time by psychiatrists, and 35.2% (n = 1159) had a psychiatric hospitalization in the prior 12-months, with over 80% of these occurring within 2 days of the index diagnosis, suggesting that these individuals were likely hospitalized during the same episode of care. In the 12 months prior to the index diagnosis of unspecified psychotic disorder, 13.9% (n = 458) had a diagnosis of a substance use disorder and half (n = 1,633, 49.6%) were diagnosed with a mood or anxiety disorder. Personality disorders and substance-induced psychosis were less frequent diagnoses in 4.6% (n = 151) and 1.6% (n = 53), respectively. A prior diagnosis of unspecified psychotic disorder was present in 10.5% (n = 346) of the cohort.

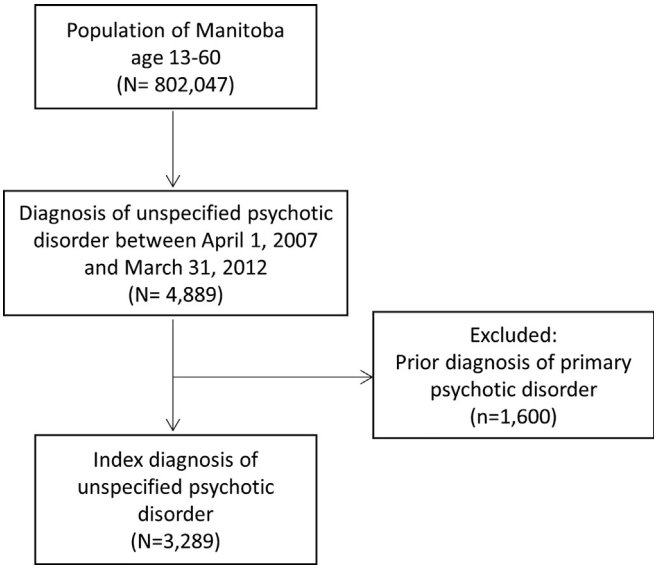

Fig. 1. Creation of the cohort.

Table 1
Baseline characteristics for all individuals with an index diagnosis of unspecified psychotic disorder, N = 3289.

Variable	No. (%) or mean (SD)
Age, mean (SD)	36.3 (15.2)
Sex, No. (%)	
Male	1746 (53.1)
Female	1543 (46.9)
Region, No. (%)	
Rural	1087 (33.1)
Urban	2202 (67.0)
Area level income[a], No. (%)	
Low	1817 (55.2)
High	1472 (44.8)
Prior 12-month hospitalization[b], No. (%)	
Yes	1159 (35.2)
No	2130 (64.8)
Prior diagnosis of unspecified psychotic disorder, No. (%)	
Yes	346 (10.5)
No	2943 (89.5)
Prior 12-month substance use disorder diagnosis, No. (%)	
Yes	458 (13.9)
No	2831 (86.1)
Prior 12-month personality disorder diagnosis, No. (%)	
Yes	151 (4.6)
No	3138 (95.4)
Prior 12-month mood or anxiety disorder diagnosis, No. (%)	
Yes	1633 (49.6)
No	1656 (50.4)
Prior 12-month substance-induced psychosis diagnosis, No. (%)	
Yes	53 (1.6)
No	3236 (98.4)
Provider making index diagnosis, No. (%)	
Psychiatrist	1522 (46.3)
Family physician	1397 (42.4)
Non-psychiatrist specialist physician	361 (11.0)
Nurse practitioner	9 (0.3)

[a] Low income refers to the lowest 2 quintiles based on neighborhood income, while high income is the remaining 3 quintiles.
[b] Includes index date.

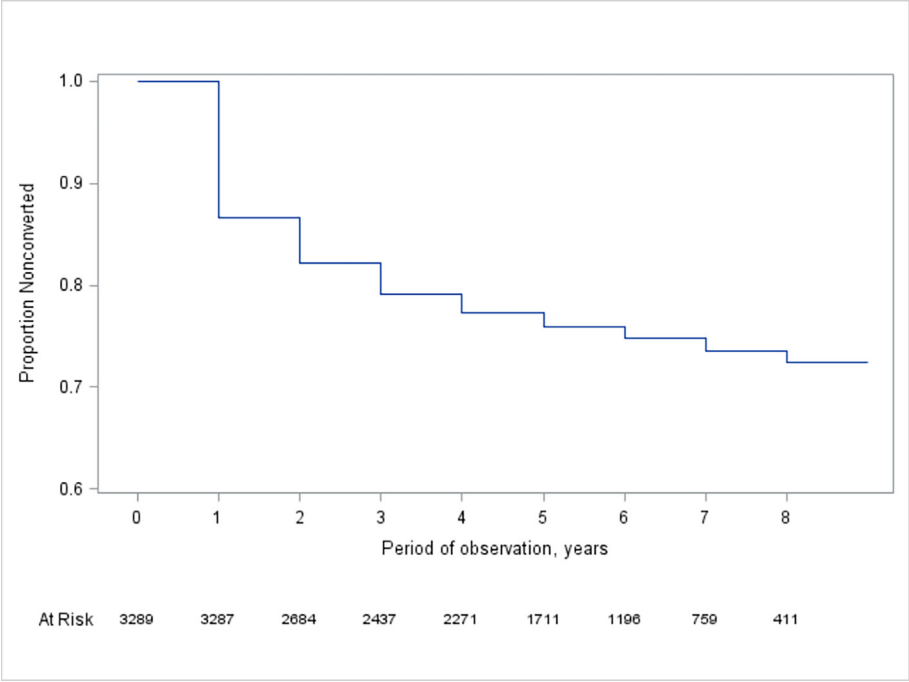

Fig. 2. Survival analysis with censoring illustrating the proportion of individuals who remain "nonconverted" (i.e. do not receive a future diagnosis of schizophrenia).

Table 2
Association between baseline characteristics and a future diagnosis of schizophrenia.

Variable	No schizophrenia (n = 2501)	Schizophrenia (n = 788)	Adjusted HR[c]	95% CI	*P* Value
Age, mean (SD)	38.5 (15.0)	29.4 (13.6)	0.978	0.972, 0.983	< .001
Sex, No. (%)					
Male	1246 (49.8)	500 (63.5)	1.402	1.209, 1.625	< .001
Female	1255 (50.2)	288 (36.6)	1.000		
Region, No. (%)					
Urban	1643 (65.7)	559 (70.9)	1.142	0.975, 1.337	.10
Rural	858 (34.3)	229 (29.1)	1.000		
Area level income, No. (%)[a]					
Low	1356 (54.2)	461 (58.5)	1.094	0.949, 1.262	.22
High	1145 (45.8)	327 (41.5)	1.000		
Prior 12-month *psychiatric hospitalization, No. (%)*					
Yes	754 (30.2)	405 (51.4)	1.274	1.083, 1.499	< .01
No	1747 (69.8)	383 (48.6)	1.000		
Prior diagnosis of unspecified psychotic disorder, No. (%)					
Yes	252 (10.1)	94 (11.9)	1.038	0.833, 1.293	.74
No	2249 (89.9)	694 (88.1)	1.000		
Prior 12-month *substance use disorder diagnosis, No. (%)*					
Yes	350 (14.0)	108 (13.7)	0.872	0.698, 1.089	.23
No	2151 (86.0)	680 (86.2)	1.000		
Prior 12-month *mood or anxiety disorder diagnosis, No. (%)*					
Yes	1243 (49.7)	390 (49.5)	0.819	0.706, 0.949	< .01
No	1258 (50.3)	398 (50.5)	1.000		
Prior 12-month *personality disorder diagnosis, No. (%)*					
Yes	100 (4.0)	51 (6.5)	1.218	0.913, 1.624	.18
No	2401 (96.0)	737 (93.5)	1.000		
Prior 12-month *substance-induced psychosis*					
Yes	36 (1.4)	17 (2.2)	0.839	0.498, 1.414	.51
No	2465 (98.6)	771 (97.8)	1.000		
Provider making index diagnosis, No. (%)					
Psychiatrist[b]	941 (37.6)	581 (73.7)	2.655	2.216, 3.180	< .001
Other[d]	1560 (62.4)	207 (26.3)	1.000		

[a] Low refers to the lowest 2 quintiles; high is the top 3 quintiles.
[b] Includes family physicians, nurse practitioners and other non-psychiatrist specialist physicians.
[c] Hazard ratios (HR) for diagnostic change over time are adjusted for all variables listed.

The mean length of follow-up for the cohort was 4.5 years. The cumulative incidence of a future diagnosis of schizophrenia after the index diagnosis of unspecified psychotic disorder was 26% (n = 788), with a mean time to diagnosis of 2.0 years. The survival curve is illustrated in Fig. 2. Of note, the cumulative incidence of schizophrenia was 13% after the first year, and 26% by year 8. During the follow-up, 12.0% (n = 396) of the cohort was censored due to death, and 6.7% (n = 220) due to migration. Those who were diagnosed with

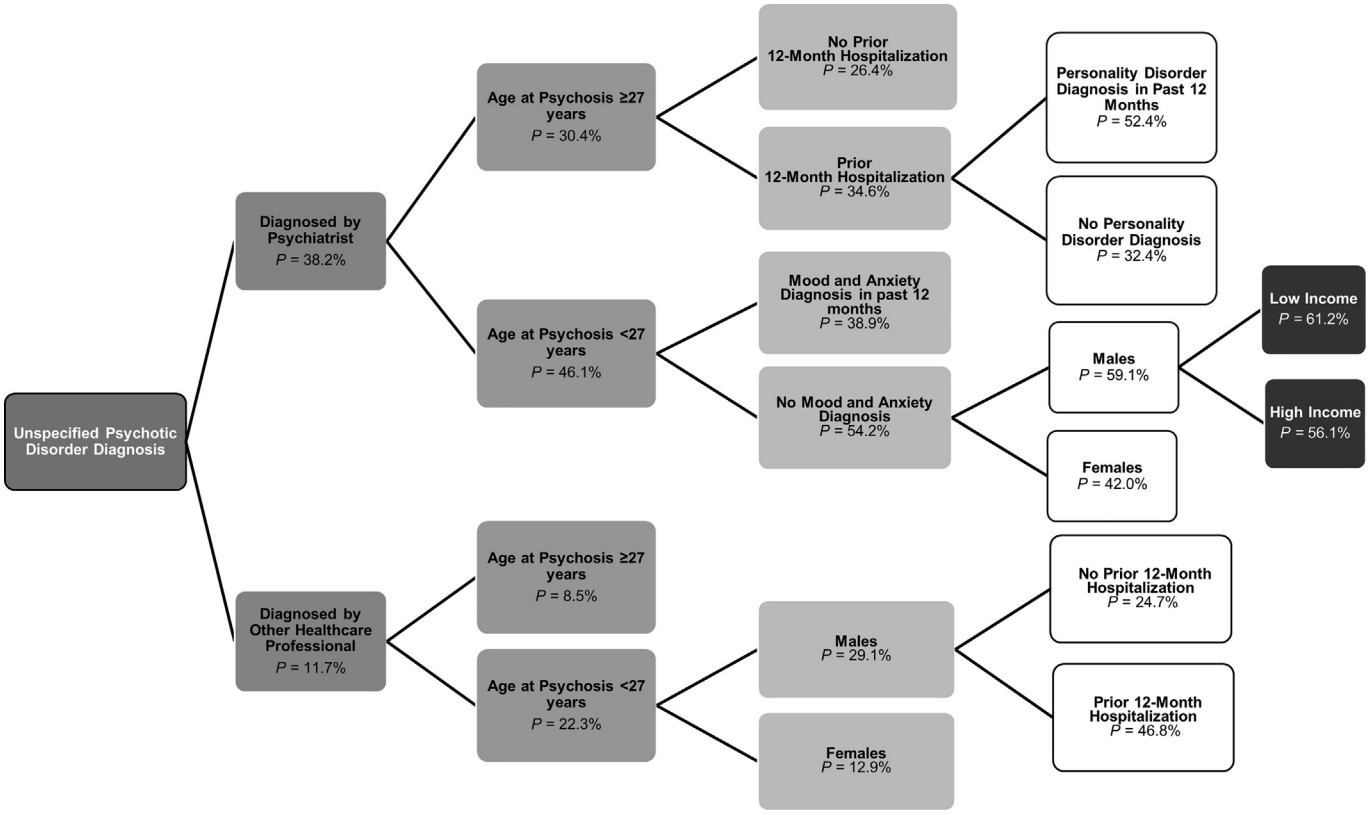

Fig. 3. Classification tree showing the probability of a future schizophrenia diagnosis after an index diagnosis of unspecified psychotic disorder.
P – indicates the proportion of people with unspecified psychotic disorder who receive a future diagnosis of schizophrenia.

schizophrenia were significantly younger on average compared to those who weren't, and more likely to be male, from an urban area, and residing in a low-income neighborhood (Table 2). Those who had a diagnosis of schizophrenia recorded in the follow-up period were also significantly more likely to have received the index unspecified psychotic disorder diagnosis from a psychiatrist, and to have had a prior 12-month psychiatric hospitalization (Table 2).

Hazard ratios (HR), adjusted for all study variables, are displayed in Table 2. The risk of a future schizophrenia diagnosis was increased for younger individuals (HR = 0.98, 95% CI 0.97–0.98), males (HR = 1.40, 95% CI 1.21–1.62), those assessed by a psychiatrist (HR = 2.65, 95% CI 2.22–3.18), and those with a prior 12-month psychiatric hospitalization (HR = 1.27, 95% CI 1.08–1.50). Those with a prior 12-month diagnosis of a mood or anxiety disorder had a lower risk of converting to a diagnosis of schizophrenia (HR = 0.82, 95% CI 0.71–0.95).

The classification tree achieved a good model fit with a misclassification rate of 0.22. Fig. 3 illustrates 9 homogenous vulnerable sub-groups of the population. Each branch that leads to a terminal node is considered a homogenous sub-group. When the diagnosis is made by a non-psychiatrist, in a female, the risk associated with a future schizophrenia diagnosis is 8.5%. By comparison, when a psychiatrist makes the diagnosis in a male, under age 27, with no mood or anxiety disorder, and who resides in a low-income neighborhood, the risk is 61.2%.

4. Discussion

To our knowledge, this is the first study to examine transition from a diagnosis of unspecified psychotic disorder to schizophrenia using North American population-level data for both inpatient and outpatient contacts with psychiatrist and non-psychiatrist health care providers. In a 5-year period, 3289 individuals (0.41% of the population of Manitoba aged 13–60) were identified as receiving a diagnosis of unspecified psychotic disorder in inpatient or outpatient settings; more than 1 in 4 of whom went on to receive a subsequent diagnosis of schizophrenia after a mean of 2 years. The highest risk of a future diagnosis of schizophrenia was found among males with the combination of a diagnosis made by a psychiatrist, before age 27, with no diagnosed mood or anxiety disorder in the prior 12-months, and residence in a low-income neighborhood.

Our cumulative rate of conversion from unspecified psychotic disorder to schizophrenia during the follow-up period is within the 95% confidence interval (0.21-0.39 for psychosis NOS) reported in the meta-analysis by Fusar-Poli et al. (2016). While that analysis included many high risk populations such as those attending early intervention programs, our rate is also very similar to the Danish and United Kingdom studies that used population-level data for secondary mental health contacts (Castagnini and Foldager, 2014; Rutigliano et al., 2018). As might be expected, we found a slightly lower total rate of conversion to schizophrenia over time compared to the Danish and United Kingdom studies (26% vs 34% and 36%, respectively). This can be explained by our inclusion of all provider diagnoses compared to psychiatric contacts only, and Canadian data based on clinicians' use of the DSM's criteria for unspecified psychotic disorder which may not be as inclusive as the ICD classification for ATPD used elsewhere (Pillmann et al., 2002). As an example, a study comparing these diagnostic categories found that a proportion of individuals diagnosed with ATPD according to ICD-10 were classified as schizophreniform disorder when DSM-IV criteria were applied (Jorgensen et al., 1996). As such, in our study, schizophreniform disorder was excluded from the definition of unspecified psychotic disorder based on administrative data codes.

In our adjusted model, the index diagnosis made by a psychiatrist was the strongest predictor of a future schizophrenia diagnosis, likely reflecting severity of symptoms and potentially time course since specialist consultations typically require a hospital presentation or referral

from another provider. Consistent with other work, we found younger age and male gender to be significant risk factors for diagnostic change to schizophrenia over time (Queirazza et al., 2014; Fusar-Poli et al., 2017b). Similar to our findings, studies examining the co-occurrence of other diagnoses have reported high rates of personality disorders (Jorgensen et al., 1996), mood and especially anxiety disorders in first episode psychosis samples (Pope et al., 2013). Other studies have also found that the presence of affective symptoms at the time of the index psychosis presentation is more often associated with resolution or conversion to affective spectrum disorders (eg. bipolar disorder) (Salvatore et al., 2009), in keeping with our finding that a prior mood or anxiety diagnosis was protective against a future schizophrenia diagnosis. Data on the association between substance use and diagnostic change has been mixed (Fusar-Poli et al., 2016).

We also observed a notable mortality rate in our sample. This rate is comparable to rates reported among individuals diagnosed with ATPD in data from Denmark, particularly young males (Castagnini and Bertelsen, 2011). A high rate of unnatural cause of death including accidents and suicides was observed among those with ATPD. We did not examine cause of death in our study.

4.1. Strengths and limitations

This population-based study afforded longitudinal linkage of health administrative data from inpatient and outpatient settings served by all providers for all residents of Manitoba, Canada. We restricted our cohort to individuals between 13 and 60 years of age, and results may not be generalizable to cases of very late onset schizophrenia (onset > age 65), which accounts for a minority of cases and experts feel likely represents a different pathophysiology (Folsom et al., 2006). Some limitations were present with the diagnostic codes, particularly with the use of the truncated ICD-9 coding system, that may have resulted in inclusion of a small number of outcomes that may not have represented true schizophrenia. However, diagnoses such as schizoaffective disorder have been shown to be more unstable, and often a later diagnosis of schizophrenia is made at some point (Sara et al., 2014).

The diagnoses used in this study relied on health service use captured in the administrative databases. There may be disparities in who accesses health care for psychotic illness, with the possibility that some factors (eg. male sex) may be associated with more service use and symptoms that are more likely to be identified and diagnosed (Anderson et al., 2018b). All outpatient and inpatient data were captured, with the exception of emergency room visits where diagnoses are not captured unless a specialist consultation is performed, meaning that less severe or more transient unspecified psychotic presentations that resolved in the emergency room and did not require assessment by a psychiatrist were not captured. Similarly, it is possible that some individuals with an index diagnosis of unspecified psychotic disorder progressed in their illness but did not come into subsequent contact with health services during the study follow-up period and a future diagnosis of schizophrenia was not recorded. These issues would tend to over and underestimate, respectively, rates of future schizophrenia. While we controlled for many factors, some variables that have been previously associated with schizophrenia such as family history of psychosis (Chang et al., 2009), lower pre-morbid functioning, duration of untreated symptoms (Fusar-Poli et al., 2016), and use of antipsychotics (Wang et al., 2018) were not included in favour of factors that could be reliably extracted from the administrative data and would likely be known at the time of index diagnosis. Ethnicity and migration history also appear to be important factors in risk for psychosis (Kirkbride et al., 2008; Anderson et al., 2015), which unfortunately could not be reliably defined in the datasets used for this study.

5. Conclusions

The current findings suggest that more than 1 in 4 individuals diagnosed with unspecified psychotic disorder will receive a future diagnosis of schizophrenia after an average of 2 years. With growing evidence for early psychosis programs (Fusar-Poli et al., 2017a; Anderson et al., 2018a), and guidelines encouraging accessibility of these services (National Institute for Health and Care Excellence, 2014), this highlights the need to appropriately monitor and intervene with individuals at high risk for illness progression. Recently, data from specialized mental health settings have been used to create clinical risk tools for progression to schizophrenia over time (Cannon et al., 2016; Fusar-Poli et al., 2017b). Our work expands on the available risk calculators for clinicians working in North America and outside of secondary mental health settings or specialized clinics. These tools can function to supplement clinical assessments and aide clinicians in counselling patients about risk, determining appropriate intervention and monitoring, and targeting referral to specialized treatment programs. As our understanding of the clinical and pathophysiological attributes of the high-risk psychosis state continues to evolve, what is often a debilitating trajectory of schizophrenia can hopefully be improved, affording affected individuals a better quality of life.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data statement

The data used in this study were obtained from linked datasets contained in the Population Health Research Data Repository held at the Manitoba Centre for Health Policy (MCHP) under HIPC Project Number 2015/2016-65. OE is an analyst at MCHP and had full access to the study data. The results and conclusions are those of the authors, and no official endorsement by the MCHP, Manitoba Health, or other data providers is intended or should be inferred.

Acknowledgments

The authors acknowledge Dr. Prabath Avadhanula, MD for assistance with literature review.

Appendix A. Details of data sources and codes

Definition	Data Source	Years	Codes
Exposure			

Unspecified Psychotic Disorder	Index diagnosis of unspecified psychotic disorder during the observation period as well as 12-months prior to the index diagnosis	Hospital admission records Outpatient medical claims	April 1, 2007 to March 31, 2012 (observation period) April 1, 2006 to March 31, 2011 (prior diagnosis)	ICD-10-CA F23, F28, F29 ICD-9-CM 298
Exclusion criteria	Diagnosis of primary psychotic disorder prior to the index unspecified psychotic disorder diagnosis	Hospital admission records Outpatient medical claims	April 1, 1999 to March 31, 2007	ICD-10-CA F20, F22, F24, F25 ICD-9-CM 295, 297
Outcome				
Schizophrenia	First diagnosis of schizophrenia after the index unspecified psychotic disorder diagnosis	Hospital admission records Outpatient medical claims	April 1, 2007 to March 31, 2015	ICD-10-CA F20 ICD-9-CM 295
Prior 12-month Psychiatric Diagnoses				
Substance use disorder	Inpatient or 2 or more outpatient diagnoses in the 12 months prior to the index unspecified psychotic disorder diagnosis	Hospital admission records Outpatient medical claims	April 1, 2006 to March 31, 2011	ICD-10-CA F10-F19 (excluding those codes listed below in substance-induced psychosis), F55, Z50.2, Z50.3 ICD-9-CM 291, 292, 303, 304, 305
Personality Disorder	1 or more inpatient or outpatient diagnosis in the 12 months prior to the index unspecified psychotic disorder diagnosis	Hospital admission records Outpatient medical claims	April 1, 2006 to March 31, 2011	ICD-10-CA F21, F60, F61, F62, F69 ICD-9-CM 301
Mood or anxiety disorder	2 or more inpatient or outpatient diagnoses in the 12 months prior to the index unspecified psychotic disorder diagnosis	Hospital admission records Outpatient medical claims	April 1, 2006 to March 31, 2011	ICD-10-CA F30–34, F38, F40, F41.0–41.3, F41.8, F41.9, F42, F43, F53.0 ICD-9-CM 296, 300, 309, 311
Substance-induced psychosis	1 or more inpatient diagnosis in the 12 months prior to the index unspecified psychotic disorder diagnosis	Hospital admission records	April 1, 2006 to March 31, 2011	ICD-10-CA F11.5, F12.5, F13.5, F14.5, F15.5, F16.5, F18.5, F19.5

ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification.
ICD-10-CA: International Classification of Diseases, 10th revision, Canada.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Publishing, Arlington, Virginia.

Anderson, K.K., Norman, R., MacDougall, A., Edwards, J., Palaniyappan, L., Lau, C., et al., 2018a. Effectiveness of early psychosis intervention: comparison of service users and nonusers in population-based health administrative data. Am. J. Psychiatry 175 (5), 443–452.

Anderson, K.K., Norman, R., MacDougall, A.G., Edwards, J., Palaniyappan, L., Lau, C., et al., 2018b. Disparities in access to early psychosis intervention services: comparison of service users and nonusers in health administrative data. Can. J. Psychiatr. 63 (6), 395–403.

Anderson, K.K., Cheng, J., Susser, E., McKenzie, K.J., Kurdyak, P., 2015. Incidence of psychotic disorders among first-generation immigrants and refugees in Ontario. CMAJ (Can. Med. Assoc. J.) 187 (9), E279–E286.

Breitborde, N.J., Bell, E.K., Dawley, D., Woolverton, C., Ceaser, A., Waters, A.C., et al., 2015. The Early Psychosis Intervention Center (EPICENTER): development and six-month outcomes of an American first-episode psychosis clinical service. BMC Psychiatry 15, 266.

Cannon, T.D., Yu, C., Addington, J., Bearden, C.E., Cadenhead, K.S., Cornblatt, B.A., et al., 2016. An individualized risk calculator for research in prodromal psychosis. Am. J. Psychiatry 173 (10), 980–988.

Castagnini, A., Foldager, L., 2014. Epidemiology, course and outcome of acute polymorphic psychotic disorder: implications for ICD-11. Psychopathology 47 (3), 202–206.

Castagnini, A.C., Bertelsen, A., 2011. Mortality and causes of death of acute and transient psychotic disorders. Soc. Psychiatr. Psychiatr. Epidemiol. 46 (10), 1013–1017.

Chang, W.C., Pang, S.L., Chung, D.W., Chan, S.S., 2009. Five-year stability of ICD-10 diagnoses among Chinese patients presented with first-episode psychosis in Hong Kong. Schizophr. Res. 115 (2–3), 351–357.

Folsom, D.P., Lebowitz, B.D., Lindamer, L.A., Palmer, B.W., Patterson, B.L., Jeste, D.V., 2006. Schizophrenia in late life: emerging issues. Dialogues Clin. Neurosci. 8 (1), 45–52.

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., et al., 2012. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatr. 69 (3), 220–229.

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rossler, A., Schultze-Lutter, F., et al., 2013. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70 (1), 107–120.

Fusar-Poli, P., Cappucciati, M., Rutigliano, G., Heslin, M., Stahl, D., Brittenden, Z., et al., 2016. Diagnostic stability of ICD/DSM first episode psychosis diagnoses: meta-analysis. Schizophr. Bull. 42 (6), 1395–1406.

Fusar-Poli, P., McGorry, P.D., Kane, J.M., 2017a. Improving outcomes of first-episode psychosis: an overview. World Psychiatr. 16 (3), 251–265.

Fusar-Poli, P., Rutigliano, G., Stahl, D., Davies, C., Bonoldi, I., Reilly, T., et al., 2017b. Development and validation of a clinically based risk calculator for the transdiagnostic prediction of psychosis. JAMA Psychiatry 74 (5), 493–500.

Gaebel, W., Zielasek, J., Cleveland, H.R., 2012. Classifying psychosis–challenges and opportunities. Int. Rev. Psychiatry 24 (6), 538–548.

Heslin, M., Lomas, B., Lappin, J.M., Donoghue, K., Reininghaus, U., Onyejiaka, A., et al., 2015. Diagnostic change 10 years after a first episode of psychosis. Psychol. Med. 45 (13), 2757–2769.

Jorgensen, P., Bennedsen, B., Christensen, J., Hyllested, A., 1996. Acute and transient psychotic disorder: comorbidity with personality disorder. Acta Psychiatr. Scand. 94 (6), 460–464.

Jutte, D.P., Roos, L.L., Brownell, M.D., 2011. Administrative record linkage as a tool for public health research. Annu. Rev. Public Health 32, 91–108.

Kirkbride, J.B., Barker, D., Cowden, F., Stamps, R., Yang, M., Jones, P.B., et al., 2008. Psychoses, ethnicity and socio-economic status. Br. J. Psychiatry 193 (1), 18–24.

Kurdyak, P., Lin, E., Green, D., Vigod, S., 2015. Validation of a population-based algorithm to detect chronic psychotic illness. Can. J. Psychiatr. 60 (8), 362–368.

Lemon, S.C., Roy, J., Clark, M.A., Friedmann, P.D., Rakowski, W., 2003. Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. Ann. Behav. Med. 26, 172–181.

Malla, A., Joober, R., Iyer, S., Norman, R., Schmitz, N., Brown, T., et al., 2017. Comparing three-year extension of early intervention service to regular care following two years of early intervention service in first-episode psychosis: a randomized single blind clinical trial. World Psychiatr. 16 (3), 278–286.

Mors, O., Perto, G.P., Mortensen, P.B., 2011. The Danish psychiatric central research register. Scand. J. Publ. Health 39 (7 Suppl. l), 54–57.

National Institute for Health and Care Excellence, 2014. Psychosis and Schizophrenia in

Adults: Prevention and Management (Clinical Guideline [CG178]). https://www.nice.org.uk/guidance/CG178.
Pillmann, F., Haring, A., Balzuweit, S., Blöink, R., Marneros, A., 2002. The concordance of ICD-10 acute and transient psychosis and DSM-IV brief psychotic disorder. Psychol. Med. 32 (3), 525–533.
Pope, M.A., Joober, R., Malla, A.K., 2013. Diagnostic stability of first-episode psychotic disorders and persistence of comorbid psychiatric disorders over 1 year. Can. J. Psychiatr. 58 (10), 588–594.
Queirazza, F., Semple, D.M., Lawrie, S.M., 2014. Transition to schizophrenia in acute and transient psychotic disorders. Br. J. Psychiatry 204, 299–305.
Roos, L.L., Gupta, S., Soodeen, R.A., Jebamani, L., 2005. Data quality in an information-rich environment: Canada as an example. Can. J. Aging 24 (Suppl. 1), 153–170.
Rutigliano, G., Merlino, S., Minichino, A., Patel, R., Davies, C., Oliver, D., et al., 2018. Long term outcomes of acute and transient psychotic disorders: the missed opportunity of preventive interventions. Eur. Psychiatry 52, 126–133.
Salvatore, P., Baldessarini, R.J., Tohen, M., Khalsa, H.M., Sanchez-Toledo, J.P., Zarate Jr., C.A., et al., 2009. McLean-Harvard International First-Episode Project: two-year stability of DSM-IV diagnoses in 500 first-episode psychotic disorder patients. J. Clin. Psychiatry 70 (4), 458–466.
Sara, G., Luo, L., Carr, V.J., Raudino, A., Green, M.J., Laurens, K.R., et al., 2014. Comparing algorithms for deriving psychosis diagnoses from longitudinal administrative clinical records. Soc. Psychiatr. Psychiatr. Epidemiol. 49 (11), 1729–1737.
Wang, H.Y., Guo, W.J., Li, X.J., Tao, Y.J., Meng, Y.J., Wang, Q., et al., 2018. Higher required dosage of antipsychotics to relieve the symptoms of first-onset Acute and Transient Psychotic Disorder (ATPD) predicted the subsequent diagnostic transition to schizophrenia: a longitudinal study. Schizophr. Res. 193, 461–462.
World Health Organization, 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. World Health Organization, Geneva.