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Patients with first-episode psychosis

The impact of established risk factors for psychosis on the 3-year outcomes

Philippe Golay[abc], Elsa Reitzel[b], Philippe Conus[b]
[a] Community Psychiatry Service, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Switzerland
[b] General Psychiatry Service, Treatment and early Intervention in Psychosis Programme (TIPP–Lausanne), Lausanne University Hospital and University of Lausanne, Switzerland
[c] Institute of Psychology, Faculty of Social and Political Science, University of Lausanne, Switzerland

Summary

Many factors increasing the risks of developing psychosis have been identified. However, it is not known whether specific factors are linked to specific clinical profiles and outcomes, and whether the number of factors affecting the same patient correlates with their clinical profile, outcomes and treatment needs.

The present study aimed to document the prevalence of risk factors and assess their clinical and outcome correlates in the early phases of psychosis. We used data from 269 patients in the prospective cohort of the Treatment and early Intervention in Psychosis Programme (TIPP), which offers 3 years of specialised treatment to young patients with first-episode psychosis. Relationships between risk factors (e.g., family history of schizophrenia or psychiatric illness, personal psychiatric history, migration in adversity, cannabis use, tobacco use, exposure to trauma), clinical presentation and various dimensions of outcome were assessed.

The most common risk factors in this cohort of early psychosis patients were a family history of psychiatric illness (64.0%), a personal history of previous psychiatric disorders (53.6%), tobacco use (44.1%) and cannabis use (39.2%). Although some risk factors (e.g., family history of schizophrenia, personal psychiatric history) had no impact on the outcomes selected, others (e.g., migration in adversity, cannabis use, tobacco use and trauma) were associated with poorer symptomatic and functional outcomes.

Results suggest that factors inducing an increased risk of developing psychosis also affect clinical presentation and outcome. Those risks should, therefore, be assessed at baseline and considered when defining treatment strategies.

Keywords: early psychosis; risk factors; psychotic disorders; outcome

Introduction

Several risk factors for psychosis in general, and for schizophrenia in particular, have been identified. These can be separated into genetic and environmental risk factors. Genetic risk is well-established: there is a 10-fold increase in risk for people with a first-degree relative with schizophrenia [1] and the concordance for monozygotic twins ranges from 40–50% [2] compared with 10–15% for dizygotic twins. In addition, several studies have shown that the incidence of psychosis is higher among children whose parents have another psychiatric illness [3, 4].

Environmental risk factors include (but are not limited to) high paternal age, gender, prenatal or perinatal factors such as the season of birth [10, 11], prenatal infections [12], maternal [13, 14] or postnatal [15] deficiencies, toxic factors [16, 17] and obstetric factors [18]. Other environmental factors include exposure to trauma [19] and the age at which that trauma occurs (the earlier the trauma occurs, the higher the risk of psychosis) [20], living in an urban environment (also referred to as urbanicity) [21, 22] and cannabis use [23]. Similarly to exposure to trauma, the risk of psychosis increases the earlier the onset of cannabis use [24], particularly if it starts before 15 years old [25]. Similarly, tobacco use is also considered a risk factor for psychosis [26, 27] and the risk also seems to increase with earlier use [28]. Finally, factors linked to migrant status, whether first or second generation [29, 30], have also been highlighted.

The invidual impact of these risk factors on the risk of developing psychosis have been extensively studied. Studies have also shown that multiplicative models are better suited than additive models to describing how two risk factors might influence the occurrence of psychosis [31]. A multiplicative (or interaction) effect occurs when the effect produced by the simultaneous occurrence of two factors is greater than the sum of the effects produced by either factor individually. Indeed, two studies have described how the onset of psychosis occurred much earlier when several environmental risk factors were present [32, 33].

Some of these factors have been studied for their impact on symptoms, functioning or the course of psychosis after onset. For example, studies have shown that patients with psychosis who had experienced trauma had poorer functioning [34–36]. More specifically,

sexual abuse appears to lead to poor social and occupational functioning [37, 38]. The occurrence of trauma at a young age seems to further impair the functioning of psychotic patients [39] and to have a deleterious influence on symptoms [40]. However, to the best of our knowledge, no studies have investigated whether the accumulation of risk factors in a single individual affects the clinical presentation of psychosis or its evolution, in addition to increasing the risks of developing a psychotic disorder.

The present study's goal was, therefore, to evaluate the relationships between various risk factors and the clinical presentations and outcomes of patients treated for a first psychotic episode. We also wanted to assess the potential interaction effects between the different risk factors and thus identify possible specific treatment needs depending on the risk factors observed in a particular patient.

Materials and methods

Procedure

The Treatment and early Intervention in Psychosis Programme (TIPP) is a specialised early psychosis programme run by the Department of Psychiatry at Lausanne University Hospital, in Switzerland [41]. Eligibility for the TIPP requires being aged from 18–35, living in the programme's catchment area (population about 350,000) and meeting the criteria for psychosis as defined by the "psychosis threshold" subscale in the Comprehensive Assessment of At-Risk Mental States (CAARMS) instrument [42]. This psychotic disorder threshold is defined by the presence of clear psychotic symptoms such as delusions, hallucinations and thought disorders, persisting for longer than 1 week with a frequency of at least three to six times a week for longer than 1 hour each time or daily for less than 1 hour each time. These are standard and widely used criteria for a first-episode psychosis threshold [43]. Patients are referred to the programme by the hospital, general practitioners, social professional networks or families. Therefore, the study sample is likely representative of the entire population of patients with early psychosis who need specialised psychiatric treatment. Patients are referred to other treatment programmes if they have an intellegence quotient below 70, have been taking an antipsychotic drug treatment for more than 6 months, or have a known intoxication-induced psychosis or brain damage.

All patients treated within the TIPP are fully assessed at baseline, after 2 months, 6 months, and then prospectively every 6 months to monitor outcomes and adjust treatments. Case managers complete a specially designed questionnaire (the TIPP Initial Assessment Tool: TIAT, available upon request) for each patient enrolled, assessing their demographic characteristics, past medical history, exposure to life events, and symptoms and functioning. It is completed using information gathered from patients and their families in the first weeks of treatment and can be updated during follow-up if new information emerges.

A psychologist and a case manager conduct follow-up assessments exploring various aspects of treatment, comorbidities and the evolution of the psychopathology and functional level at baseline and after 2, 6, 12, 18, 24, 30 and 36 months of treatment. Symptom assessments are conducted by a psychologist who has received standardised training but is not involved with the patients' treatment. TIPP case managers remain available for each patient up to twice a week for 3 years. An intensive case management team can provide additional support and treatment at any time during the treatment period, with case managers remaining involved to ensure continuity of care.

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Canton of Vaud (CER-VD; protocol #2020-00272). Access to clinical data was granted for research purposes, allowing the data generated during patient follow-up to be used in the study. Consequently, all the patients who received treatment within the TIPP at that time could be included in this study, suggesting again a highly representative sample of early psychosis patients.

Measures

Case managers and an experienced psychologist performed detailed patient evaluations using interviews and the TIAT questionnaire. Based on the risk factors highlighted in the literature, we were able to record many factors for this cohort.

Genetic risk markers included having a family history of psychosis or psychiatric illness. These variables considered first- and second-degree family members. Personal histories of psychiatric disorders other than psychosis, according to the DSM-IV criteria [44], were also considered.

Environmental risk factors recorded were migration in adversity (based on an anamnesis of involuntary migration linked to politics, violence or escaping poverty), having experienced trauma (sexual and physical abuse before the ages of 16 or 12 [39], cannabis use (according to DSM-IV criteria for abuse and dependence), cannabis dependence and abuse before the age of 14, tobacco use (according to DSM-IV criteria for abuse and dependence) [44].

Outcomes

The correlations of these risk factors with patients' clinical presentation and outcomes were assessed for three time periods: (1) impact on the acute phase of the illness or a psychotic crisis, referred to here as the "baseline situation"; (2) impact during the 3-year follow-up period; and (3) impact at the end of the 36-month follow-up.

Two different outcomes were assessed at baseline: (1) the highest Clinical Global Impression scale score (CGI) [45] as a marker of the most symptomatic time point (defined here as the "worst" moment of the psychosis); and (2) the lowest level of functioning according to the Global Assessment of Functioning (GAF), which is rated on a scale from 1–100 [44].

During the 3-year follow-up period, the outcomes were the patient's engagement with their care, the markers of being either lost to follow-up for at least 2 months or permanently lost to follow-up before the end of the 3 years, and whether or not they had made a suicide attempt.

For situations at the end of the follow-up, we relied on symptomatic recovery according to Andreasen's criteria for the patient's last Positive and Negative Syndrome Scale (PANSS) score in their last year of the programme (mild or lower (≤3) score on the following items: delusion, unusual thought content, hallucinatory behaviour, conceptual disorganisation, mannerisms, blunted affect, social withdrawal and lack of spontaneity; [46]). We also used the CGI scales and considered that the patient had recovered if their final score was ≤3 [47].

To assess functional recovery, we evaluated patients using the Modified Vocational Status Index and the Modified Location Code Index (MVSI and MLCI) [48]. Patients were considered as living independently based on their MLCI score (head of household or living alone, living with a partner or peers or living with their family with minimal supervision). Patients were considered to be working based on their MVSI score (in paid or unpaid, full- or part-time employment, being an active student in school or university, head of household with an employed partner [homemaker], or a full- or part-time volunteer). Functional recovery was defined as a GAF score >70. Functional recovery was defined as a final Premorbid Adjustment Scale (PAS) [49] score equal to or lower than the premorbid rating on four of the five general PAS scale's items (50). Items on education and abruptness in the change in

work were ignored as they could not have changed during the period of interest (51).

Statistical analysis

First, the prevalence of each risk factor was computed to assess its relevance to the following analyses. Then, to identify risk factors with a potential impact, we used simple linear and logistic regression models, with each risk factor as the independent variable and each outcome as the dependant variable. The results of these simple regression analyses were used to select the factors likely to be related to the different outcomes. Risk factors associated with p-values <0.05 were considered significant, and those associated with a p-value < 0.10 were labelled trend variables. Using a stepwise input procedure, significant and trend variables were entered into multiple regression models for the outcomes they predicted, with the aim of retaining only the most important predictors. Finally, when several risk factors were significant (p-value <0.05) for the same outcome in the results of a multiple regression model, we tried to highlight possible interaction effects by introducing the product of the two variables into an additional model. This enabled us to verify whether the co-occurrence of two risk factors produced a stronger effect than the addition of two independent effects. All analyses were performed using IBM SPSS 23 software. All statistical tests were two-sided, and significance was set at $\alpha = 0.05$.

Results

A total of 269 patients were included, with a mean age of 24.3 years at baseline. They were mostly men (66.9%), and their parents' socioeconomic statuses (defined as low, intermediate or high [52]) were mostly intermediate and high (44.2% and 38.3%, respectively). On average, they had completed 9.8 years of school. Their final diagnoses were schizophrenia (60.2%; 162), schizophreniform disorders (9.7%; 26), schizoaffective disorders (10.0%; 27), bipolar disorder (7.8%; 21), major depression with psychotic symptoms (2.2%; 6) and other diagnoses (10.0%; 27).

Frequency of risk factors

The risk factors of a family history of psychiatric illness (64.0%; 158) and a personal history of psychiatric illness (53.6%; 142) were present among more than half of the patients. The risk factors of tobacco use (44.1%; 116), cannabis use (39.2%; 100), migration in adversity (27.2%; 50), trauma (26.5%; 71) and a family history of schizophrenia (25.6%; 53) were present in more than a quarter of the cohort. The prevalence of the remaining risk factors was lower: trauma before 12 years old (13.4%; 36) and cannabis use before 14 years old (7.5%; 19).

Table 1: Cumulative risk factors

Number of risk factors per patient	Frequency, % (N)	Cumulative frequency, %
0	9.3 (25)	9.3
1	18.2 (49)	27.5
2	19.0 (51)	46.5
3	19.3 (52)	65.8
4	17.1 (46)	82.9
5	10.4 (28)	93.3
6	4.8 (13)	98.1
7	1.5 (4)	99.6
8	0.4 (1)	100

Cumulative risk factors

More than 50% of the patients had at least three risk factors, and only 9.3% had none of the risk factors in the study (table 1).

Baseline presentation

Correlates with the Clinical Global Impression scale's maximum score

The maximum CGI score was only significantly related to migration in adversity ($\beta = 0.16$; $p = .047$), which explained about 2.5% of the score's variance.

Correlates with the Global Assessment of Functioning's lowest level

A family history of psychiatric illness ($\beta = -0.18$; $p = .009$) and trauma before 12 years old ($\beta = -0.14$; $p = .036$) predicted the worst lifetime GAF, and trauma could be considered a trend factor ($\beta = -0.12$; $p = .061$). After introducing these three factors into a multiple regression model, the only significant risk factor remaining was a family history of psychiatric illness ($\beta = -0.18$; $p = .009$), which explained about 3% of the score's variance.

Situation during the programme

Prediction of patients' engagement with their care and suicidality

None of the risk factors was significantly associated with patients' engagement with their care or with suicidality.

Correlates with the patient's situation at the end of the follow-up

Symptomatic recovery based on the PANSS (Andreasen's Criteria)

Several factors were significantly correlated with poorer symptom recovery, including cannabis use (Odds Ratio = 0.42; $p = .012$), migration in adversity (OR = 0.34; $p = .017$), tobacco use (OR = 0.48; $p = .026$) and a family history of schizophrenia (OR = 0.45; $p = .041$). Two factors could be considered as being at a trend level: cannabis before 14 years old (OR = 0.23; $p = .069$) and trauma before 12 years old (OR = 0.44; $p = .095$). When introduced simultaneously into a multiple regression model, the three risk factors of migration in adversity (OR = .013; $p = .002$), cannabis use (OR = 0.19; $p = .005$) and trauma before 12 years old (OR = 0.22; $p = .049$) remained significant, together explaining 32.8% of the score's variance.

Symptomatic recovery (final CGI)

The three risk factors of trauma (OR = 0.22; $p = .002$), trauma before 12 years old (OR = 0.15; $p = .005$) and tobacco use (OR = 0.38; $p = .025$) were significantly related to symptomatic recovery. In the multiple regression model, only the risk factor of trauma remained significant (OR = 0.23; $p = .002$), which explained 14.2% of the scale score's variance.

Functional recovery (work)

The four risk factors of tobacco use (OR = 0.37; $p = .004$), trauma (OR = 0.33; $p = .011$), cannabis use (OR = 0.39; $p = .012$) and trauma before 12 years old (OR = 0.10; $p = .024$) were significantly related to functional recovery for work. A family history of psychiatric illness

Table 2: Results summary

	Family history of psychiatric illness	Family history of schizophrenia	Personal psychiatric history	Migration in adversity	Trauma	Trauma before 12 y	Cannabis	Cannabis before 14 y	Tobacco
Initial situation									
Maximum CGI									
Minimum GAF	+								
Engagement with care: loss of sight									
More than 2 months									
Definitively									
Suicide attempts									
Symptomatic response									
PANSS (Andreassen)				+		+	+		
Final CGI					+				
Functional recovery									
Work						+			+
Independent living									
Work & Independent living					+		+		
GAF				+			+		
PAS									
Total	1	0	0	2	2	2	3	0	1

+ = significant association.

(OR = 0.52; p = .054) was only significant at the trend level. In the multiple regression model, only the two factors of trauma before 12 years old (OR = 0.13; p = .050) and tobacco use (OR = .035; p = .004) remained significant, explaining 13.4% of the score's variance.

Functional recovery (independent living)

None of the risk factors was significantly related to functional recovery. Tobacco use was significant at the trend level (OR = 1.76; p = .051).

Functional recovery (work & independent living combined)

The four factors of trauma (OR = 0.20; p = .004), tobacco use (OR = 0.45; p = .026), family history of psychiatric illness (OR = 0.47; p = .035) and cannabis use (OR = 0.45; p = .041) were all significantly related to combined functional recovery. In the multiple regression model, only trauma (OR = 0.15; p = .002) and cannabis use (OR = 0.41; p = .024) remained significant, explaining 14.9% of the score's variance. Trauma before 12 years old and cannabis use before 14 years old could not be introduced into the regression models because none of the patients in the database with these risk factors met the combined criteria for recovery, rendering a statistical estimation of the parameters impossible. Nevertheless, the recovery ratios compared with Fisher's exact test showed a significant association: p = .002 for trauma before 12 years old and p = .026 for cannabis use before 14 years old. Unfortunately, these two factors could not be included in the multivariate analysis.

Functional recovery (GAF)

Four risk factors significantly predicted functional recovery but at the trend level only: migration in adversity (OR = 0.41; p = .059), trauma before 12 years old (OR = 0.30; p = .060), cannabis use (OR = 0.51; p = .061) and tobacco use (OR = 0.56; p = .074). The two risk factors of migration in adversity (OR = 0.26; p = .013) and cannabis use (OR = 0.27; p = .011) were significant in the multiple regression model, explaining a combined 15.6% of the score's variance.

Functional recovery (PAS)

None of the risk factors predicted functional recovery according to the PAS.

Interactions between risk factors

None of the multiple regression models was able to reveal any significant statistical interactions between the risk factors themselves. In other words, the joint presence of these factors had no multiplicative effect over and above the sum of the single effects.

Results summary

Certain risk factors had significant relationships with several outcomes (Table 2). Migra-

tion in adversity was related to patients' characteristics at the baseline clinical presentation and to their symptomatic and functional response.

Cannabis use, having experienced trauma and trauma at a young age all influenced the symptomatic and functional responses. Smoking tobacco, on the other hand, was only related to functional recovery, and a family history of psychiatric illness was only related to the baseline situation. The other risk factors (family history of schizophrenia, personal history of psychiatric illness and cannabis use before 14 years old) had no significant relationships with any of the outcomes.

Discussion

According to our results, many of the known risk factors for psychosis are highly prevalent in early psychosis patients, and some of them seem to have a substantive influence on their outcomes. The outcomes best predicted by the risk factors were symptomatic recovery (especially according to the PANSS scale, with the largest effect size) and functional recovery. Patients' baseline situations, i.e. at the time of their first 'psychotic episode', seemed to be less influenced by risk factors. One hypothesis for this is that the clinical picture at the time of the psychotic episode is of such intensity in all patients that it is difficult to highlight any reliable differences between them.

On the other hand, about half of the recognised risk factors studied were not significant predictors of any of the outcomes, namely a family history of schizophrenia, a personal psychiatric history and cannabis use before 14 years old. This means that although they play a role in the risk of schizophrenia, they do not seem to be related to outcomes after the onset of psychosis.

Symptomatic and functional recovery were only predicted by environmental factors (migration in adversity, trauma, trauma before 12 years old, cannabis use and tobacco use). The baseline situation, on the other hand, was the only outcome seemingly influenced by a genetic risk factor (a family history of psychiatric illness was associated with a low GAF score), but it was also predicted by the environmental factor of migration in adversity (associated with a maximal CGI scale score). The presence of environmental risk factors may suggest an increased risk of a more intense acute phase of psychosis and especially of presenting with a poor symptomatic or functional evolution. Genetic risk markers, particularly a family history of psychiatric illness, were the only risk factors associated with a lower level of functioning in acute-phase psychosis.

Cannabis use, migration in adversity and trauma were significant risk factors, especially trauma, which is in line with other studies (37-40). Early onset of trauma (before age 12) also successfully predicted symptomatic (PANSS) and functional (work) outcomes, which is also consistent with the existing literature on the particular role of early trauma (39, 40).

None of the recognised risk factors was a predictor of suicide attempts or engagement with care during the TIPP. It is difficult to definitively state whether no risk factors were associated with engagement with care or whether our selected outcomes (suicide attempts, lost to follow-up for two months and lost to follow-up for more than one year) were inadequate. In another study of the same cohort, we found that only three variables were related to disengagement with the programme (a low socio-economic status, patients who had committed offences and a diagnosis of schizophreniform or brief psychotic disorder). This could, however, be due to the very low overall level of disengagement with the programme and the limited sample size in this patient sub-group (53).

One of this study's hypotheses was that there could be multiplicative effects between risk factors. However, no statistical interactions between significant risk factors were found in any of the multiple regression models. In other words, risk factors did not seem to interact with each other to produce greater effects when present simultaneously. However, the absence of such interaction effects does not exclude the idea of the accumulation of individual effects, and it remains preferable to be affected by one risk factor rather than several.

This work has several clinical implications. Migration in adversity, trauma and trauma before 12 years old were the most important risk factors.; they all generate stress and may point to socially precarious populations. These results should encourage clinicians to be watchful for the specific needs of such target populations, which could benefit from reinforced care to prevent unfavourable outcomes. Cannabis use was the best risk factor in our study for predicting both patients' functional and symptomatic evolution. Tobacco use was also implicated here as a risk factor for poor occupational outcomes. Further analysis of the associations between substances and psychosis outcomes will be necessary to focus the dissemination of important prevention messages.

The present study has some limitations. There were several recognised risk factors for psychosis whose effects could not be analysed because the TIPP does not collect data on them. The biggest data gap is probably in perinatal factors, but data on environmental factors such as growing up in an urban environment were also lacking. This research suggests that the risk factors for psychosis influence its initial presentation and outcomes, but it would be interesting to perform similar analyses on different, larger cohorts. If these results were to be confirmed, they would provide critical information for the specific management of young people who have suffered physical or sexual trauma, experienced migration in adversity or have a family history of psychiatric illness. They should also form part of the prevention messaging on the risks of cannabis and tobacco use.

Correspondence
Dr. Philippe Golay
Department of Psychiatry
Lausanne University Hospital and
University of Lausanne
Consultations de Chauderon
Place Chauderon 18
CH-1003 Lausanne
Philippe.Golay[at]chuv.ch

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Ethics approval and consent to participate
This study was carried out in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Canton of Vaud (CER-VD; protocol #2020-00272). Access to clinical data was granted for research purposes, allowing the data generated during patient follow-up to be used in the study. Consequently, all patients who received treatment within this programme could be included.

Conflicts of interest
The authors declare that they have no competing interests.

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Authors' contributions
PG and PC designed this research.
PG and ER analysed and interpreted the data.
PG and ER drafted the manuscript's first version.
PC critically revised the manuscript for important intellectual content.

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Dr. Philippe Golay
Department of Psychiatry
Lausanne University Hospital and University of Lausanne