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The Relationship between Alcohol-Cannabis Use and Stressful Events with the Development of Incident Clinical Psychosis in a Community-Based Prospective Cohort

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SUMMARY

Objective: The aim of this study is to evaluate the associations between alcohol-cannabis use and forensic/stressful events with the risk of incident clinical psychosis during follow-up.

Method: A community-based sample (n: 2142) was screened for clinical psychosis (schizophrenia and other psychotic disorders, affective disorders with psychotic features) at baseline and follow-up. Thus, *incident clinical psychosis cases* to develop during follow-up (individuals with no clinical psychosis at the baseline assessment and with clinical psychosis at the follow-up assessment) were detected (n: 27). These *cases* and the *controls* who did not report any psychotic symptoms at the follow-up assessment (n: 1691) were compared for exposure to environmental risk factors during follow-up (total n: 1718).

Results: Individuals reporting heavy alcohol drinking or cannabis use during follow-up had significantly higher risk of incident clinical psychosis. The monthly frequency of drinking and cannabis use was also associated with the risk. Higher number of stressful life events exposed predicted higher risk of incident clinical psychosis. The risk of incident clinical psychosis was significantly higher in case of coexistence of two risk factors (heavy drinking, cannabis use, ≥3 stressful events), in comparison with the existence of a single risk factor (17.7 vs. 1.6%, p<0.001).

Conclusion: Heavy drinking, cannabis use, forensic events and stressful events were associated with the risk of incident clinical psychosis. The coexistence of multiple stressful events and disorders related to abuse of alcohol/cannabis should be considered as a warning for the development of clinical psychosis.

Keywords: Psychosis, alcohol-induced disorders, marijuana smoking, life stress, forensic psychiatry

INTRODUCTION

Modern psychiatry defines psychosis, generally, as a mental state characterized by disruptions in thinking, perception and behaviour. However, psychosis is not a diagnosis itself (American Psychiatric Association 2013). Psychosis forms a wide spectrum including transient alterations in daily life to phenomena which is above the severity of need for medical care (clinical threshold). Psychosis above the clinical threshold may be present as part of a series of disorders (e.g. mood disorders with psychotic features) besides schizophrenia and other psychotic disorders (Kirli and Binbay 2018). There is substantial evidence that psychotic phenomena within different mental disorders have a series of common characteristics (Allsopp et al. 2019, van Os et al. 2019, Isvoranu et al. 2020, Kotov et al. 2020). Therefore, many recent studies have commenced to provide a combined assessment of threshold psychotic phenomena within different mental disorders. In this study, the term '*clinical psychosis*' is used in a way to include any psychotic phenomena above the clinical threshold (i.e. schizophrenia and other psychotic disorders, mood disorders with psychotic features), based on previous research (Dominguez et al. 2009). Representative community-based studies reported the prevalence of clinical psychosis from 2.5% to 3.5% (Perälä et al. 2007, Binbay et al. 2012). Schizophrenia, which is only one of the many mental disorders with clinical psychosis, causes 2.3% of the disability adjusted life years (DALY) in Turkey (Turkish Ministry of Health 2006).

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Results from recently-carried-out studies suggest a multifactorial model for the aetiology of psychosis. Other than genetic factors, several environmental factors impacting on different periods of the life span have crucial roles in the development of psychosis (van Os et al. 2010). A recent meta-analysis underlined alcohol-cannabis use and psychosocial stress as among these environmental risk factors (Linscott and van Os 2012). Many cross-sectional studies reported cannabis and alcohol as the most frequently used psychoactive substances among patients with first episode psychosis (Larsen et al. 2006, Archie et al. 2007, Lachman et al. 2012, Tulachan et al. 2014, Thungana et al. 2019). Furthermore, studies showed high rates of alcohol intake prior to first episode of psychosis, which reduced following treatment (Harrison et al. 2008, Turkington et al. 2009, Kumar et al. 2015). However, studies investigating the associations between alcohol and psychosis conducted in different regions of the world to date have produced inconsistent results. This inconsistency was explained by different alcohol use patterns and different attitudes toward alcohol use in particular regions where the studies were conducted (Tan et al. 2018, Cetty et al. 2019, Thungana et al. 2019). Therefore, further longitudinal community-based studies are needed in this area.

Research investigating the associations between cannabis and psychosis have generally produced consistent results (Marconi et al. 2016). Cannabis was reported both as a predisposing and a precipitating factor for the development of psychosis (Binbay et al. 2011a, Kuepper et al. 2011). Recent studies have shown that tetrahydrocannabinol (THC) levels are higher in current commonly used forms of cannabis than the older ones. Therefore, cannabis use might further increase the risk of psychosis in our days than before (Freeman et al. 2018, Potter et al. 2018, Di Forti et al. 2019). These results suggest that the association between cannabis and psychosis may be a greater concern for public mental health in the near future. However, this issue is still controversial. Some authors argue that more evidence is needed to claim causal associations between cannabis and psychosis (Ksir and Hart 2016). Furthermore, the population attributable fraction (PAF) of cannabis use associated with psychosis in the community differs in various parts of the world (Ortiz-Medina et al. 2018, Di Forti et al. 2019). Therefore, longitudinal community-based studies in different regions of the world are urgently needed.

Associations between environmental risk factors and clinical psychosis have been evaluated in some cross-sectional studies in Turkey (Alptekin et al. 2009, Binbay et al. 2011a, Doğan 2011, Binbay et al. 2012, Kocal et al. 2017). However, data for the Turkish population is insufficient (Binbay et al. 2011c). As far as we know, no studies to date have longitudinally investigated environmental risk factors for clinical psychosis in a Turkish community-based population. Furthermore, a few studies worldwide have investigated the impact of coexistence of multiple risk factors on the risk of clinical psychosis (Pries et al. 2019). As a substantial part of the environmental risk factors are modifiable in nature, research on these factors is crucial.

The aim of this study is to evaluate the associations of heavy drinking, cannabis use, forensic and stressful events with the risk of incident clinical psychosis during the follow-up period. The main hypothesis of the study is that the risk of incident clinical psychosis is significantly higher in individuals exposed to these risk factors. The secondary hypothesis is that the risk of incident clinical psychosis is significantly higher in case of coexistence of multiple risk factors in comparison with the existence of a single factor.

METHODS

Sample and Study Design

The study consists of two assessments on two levels (baseline and follow-up). At the baseline assessment level, the households which are representative of the general-population were visited. An individual aged between 15 and 64 was selected from each household by random sampling, who was then interviewed (n: 4011). For the sixth year assessment, these households were re-visited. If during these visits it was found that the previously-interviewed individuals in respective households had moved and no longer resided in the same household, the participants were called on the numbers they provided during the baseline assessment. In these calls, the individuals were reminded about the baseline assessment, and then their current addresses were requested for the follow-up assessment. The individuals who provided their valid addresses were also visited at their new households. Of the individuals who could be contacted during the follow-up, 424 rejected to participate in the follow-up assessment. 44 individuals were either deceased or imprisoned. Residences in 22 addresses were demolished. 991 individuals could not be contacted because they were neither found at their baseline addresses and nor did they answer the calls. 386 individuals had moved to remote areas. As a result, 2142 individuals who were interviewed at the baseline assessment were successfully interviewed at the follow-up assessment.

The sample of this study was defined by the evaluation process for clinical psychosis conducted both at the baseline and the follow-up assessments. The evaluation process for clinical psychosis is detailed below. As the aim of this study was to assess the factors associated with the *incident clinical psychosis during follow-up*, individuals already having clinical psychosis at the baseline assessment were excluded (n: 48). The *case group* of this study (incident clinical psychosis) consisted of individuals who had clinical psychosis during the follow-up

assessment (n: 27). The *control group* consisted of individuals who did not answer 'yes' to any psychosis items at the follow-up assessment (n: 1691) (total n: 1718).

The study was approved by the local ethics committee of Izmir no: 1. Participants provided written informed consent.

Interviews and Quality Control

The methods for data quality at the baseline assessment were detailed in another previous article to ensure high-quality of field data (Binbay et al. 2011b). A similar procedure was followed for the data quality at the follow-up assessment. Lay interviewers (medical students and/or psychology graduates) used a *fully-structured* interview form. Theoretical training as well as practical training on the use of the interview form was given by experienced physicians to the interviewers. The interviewers were allowed start fieldwork after successfully completing the above-mentioned training. Information given to the interviewers included only the name, the surname and the telephone numbers of the participants. Thus, they were *blind* on the results of the baseline assessments. Each interview form was systematically reviewed by a psychiatry resident. During these reviews, sociodemographic and clinical data on the participants provided at the baseline and the follow-up assessments were compared to check accuracy and quality of the data. Furthermore, the research team held weekly meetings for detailed feedback on the fieldwork as well as on data quality. Phone interviews were allowed only in cases where the research team deemed a face-to-face interview impossible (e.g. when interviewees were found to have moved to a remote area, or inaccessible, etc.) (n: 575). In cases where interview quality was found insufficient, respective individuals were re-interviewed by a different lay interviewer (n: 21). In cases where the forms had substantial shortcomings, the research team re-interviewed respective individuals via telephone (n: 232) or during face-to-face re-interviews (n: 86).

Screening Instruments and the Independent Variables

Psychotic symptoms were screened using the Composite International Diagnostic Interview (CIDI) 2.1 (Robins 1988). CIDI has been used in various psychiatric epidemiological surveys in Turkey (Cilli and Kaya 2003, Deveci et al. 2007, Alptekin et al. 2009). As CIDI is a fully structured interview, it can used by both clinicians and non-clinicians after a training. CIDI follows a flowchart evaluating the frequency and the duration of symptoms, associated help-seeking, the history of consultations with physicians, diagnoses, and the impact on mood, social and occupational functioning. Furthermore, CIDI evaluates whether or not the symptoms are due to a somatic illness, medication, use of alcohol or other substances (Kılıç and Göğüş 1997). In this study, psychotic symptoms were screened using the following modules of the CIDI 2.1: Schizophrenia and other psychotic symptoms (module G) and the interviewer observations assessing the attitudes and behaviours associated with the psychotic disorders (negative and disorganisation symptoms, module P).

Use of alcohol and cannabis was assessed using relevant modules of the CIDI 2.1 (alcohol module J, cannabis module L). The assessment of alcohol use was based on the definition of *heavy drinking*. Heavy drinking was defined as consuming more than 14 standard drinks per week for males and more than 7 standard drinks for females. 'Standard drink' is a small can of beer (35 cl, 5%), a glass of wine or a 'shot' of spirits as raki, vodka or gin (Uluğ and Öztürk 2015)**.** Furthermore, cannabis use was assessed using the criterion of 'at least five times' based on previous research (Kuepper et al. 2011).

Stressful events were assessed using the List of Threatening Life Events Questionnaire. Based on the reliability and validity study published on 1990, the following events were taken into account (Brugha and Cragg 1990): A serious illness or injury (self-suffering or involving a close relative), loss/death of a close relative, divorce or separation in a long-term relationship, serious problems with a close relative, serious problems about work or unemployment, serious financial problems, police/court appearance or being burglarized. The questionnaire also assesses the date of events as well as their impact on the individual. The questionnaire is commonly used in psychiatry, psychology and sociology surveys which investigate the source as well as the impact of stress. The questionnaire was used in EU-GEI (European network of national schizophrenia networks studying Gene-Environment Interactions) research in Turkey. Based on previous research, a *stressful events continuous variable* was constructed and coded as the sum score of each 'yes' responses (Morgan et al. 2020). Furthermore, by the $_{\text{LSENS}}$ command in STATA, the number of stressful events (≥3) of the highest level of sensitivity and specificity for the clinical psychosis variable was calculated using ROC curves. Using this threshold, *a dichotomous stressful events variable* was constructed.

Forensic events were assessed by asking for a history of any involvement with the police or appearance before any court, including any arrests since the baseline assessment. The variable was based on self-report information and coded dichotomously.

Based on previous studies (Cougnard et al. 2007, Guloksuz et al. 2016, Pries et al. 2018), the association between the coexistence of risk factors (heavy drinking, cannabis use, stressful events- dichotomous) and the risk of clinical psychosis were assessed by the variable '*number of environmental risk factors exposed'*. The variable included four categories (0: None, 1: One of the three factors present, 2: Two of the three factors present, 3: All of the three factors present). None of

the participants had all three factors present hence the variable was either '0, 1 or 2.'

The Dependent Variable: Incident Clinical Psychosis during Follow-up

Both at the baseline and the follow-up assessments, clinical re-interviews were performed with participants meeting at least one of the following criteria: i) A self-reported history of a consultation with a physician or use of any psychotropic medication or any hospitalization due to a mental health problem ii) At least three positive psychotic symptom endorsements in the CIDI or one positive psychotic symptom endorsement plus a positive response to questions evaluating the frequency, the severity and the duration of the symptoms, associated help-seeking, or loss of functionality iii) Any positive response to the questions the interviewer observations section (CIDI module P) or any interviewer comment suggesting psychosis.

Participants who met the criteria for a clinical re-interview were invited to the research hospital. Physicians visited participants who were not available or who refused to come to the hospital at home environment. Thus, 82.2% of the probable cases were interviewed using the Structured Clinical Interview for DSM-IV Disorders (SCID). In cases where the participants could not be clinically interviewed on a face-to-face basis for having moved or due to inaccessibility etc., they were reached via telephone (n: 92). In these phone calls, a physician evaluated whether these symptoms were a part of the clinical psychosis or not. When necessary, relatives have been contacted for information on mental health of the participants, with the permission of the participants. All cases were reviewed and discussed by at least two physicians as to whether or not the symptoms were a part of the clinical psychosis.

The dependent variable *incident clinical psychosis during follow-up* was defined as *no* clinical psychosis during baseline assessments and the *presence* of clinical psychosis during follow-up assessments (n: 27).

Statistical Analysis

Stata version 13 was used for data analysis (STATA Corp 2013). First, analyses were made to assess the participation in the follow-up assessment. The respondents and the non-respondents of the follow-up assessment were compared in terms of their baseline sociodemographic characteristics (age, sex, educational level and marital status). Furthermore, the effect sizes of the differences between the respondents and non-respondents were assessed using the Cramer's *V*. Cramer's *V* values are between 0 to 1. Values closer to 0 indicate weaker associations, values closer to 1 indicate stronger ones (Cramer 1946).

In order to test the primary hypothesis, the associations between the dependent variable *incident clinical psychosis* and the independent variables *heavy drinking, cannabis use, forensic events and stressful events* were evaluated using logistic regression. Following that, the models were adjusted for *a priori*-defined sociodemographic confounders (age, sex, educational level and social insurance). Odds ratios obtained both from univariate and multivariate models were presented with their 95% confidence intervals (CI). Furthermore, associations between self-reported monthly frequencies of alcohol/cannabis use and incident clinical psychosis were analyzed using polychoric correlation coefficients.

In order to test the secondary hypothesis, associations between the variable *number of environmental risk factors exposed* and the incident clinical psychosis were assessed using logistic regression. Furthermore, the model was adjusted for age, sex, educational level and social insurance. Following that, the odds ratios (OR) of the groups exposed to a single and multiple risk factors were compared using the $_{\text{LINCOM}}$ command in STATA. The significance level was $p<0.05$ in all analyses.

RESULTS

Assessment of the Participation

Participation to the follow-up assessment of men, secondary-high school graduates, younger and non-married individuals were lower. However, the differences between the effect size of respondent and the non-respondent groups in terms of sex, age, educational level and marital status were very small (Cramer's *V* values respectively: 0.04, 0.1, 0.13, 0.15). The comparison of the baseline sociodemographic variables between the respondent and the non-respondent groups are given in Table 1.

The Associations between Alcohol-Cannabis Use, Forensic Events, Stressful Events and the Risk of Incident Clinical Psychosis during Follow-up

The associations between heavy drinking, cannabis use, forensic events, stressful events and the risk of incident clinical psychosis during follow-up are presented in Table 2. The rate of cannabis consumption among participants with incident clinical psychosis was 22.2%. This rate was 1.5% for the control group. Consequently, cannabis use during follow-up was associated with the risk of incident clinical psychosis ($OR_{adjusted}$=24.5, 95%CI: 5.4-57.2). Furthermore, the risk of incident clinical psychosis gradually increased commensurately with increased frequency of monthly cannabis use (r: 0.62, $p<0.001$). Similarly, participants who were heavy drinkers presented a significantly higher risk of incident clinical psychosis during the follow-up period

Table 1. Comparison of the Respondents with the Non-respondents at the Follow-up Assessment in terms of Age, Sex, Educational Level and Marital Status

	Non-respondents (n:1869)	Respondents (n:2142)	χ^2	p	Cramer's *V*
	n (%)	n (%)			
Sex					
Male	816 (43.7)	864 (40.4)	4.5	0.03	0.03
Female	1053 (56.3)	1278 (59.6)			
Age*					
15-24	429 (23.0)	348 (16.2)	44.2	<0.01	0.1
25-34	523 (28.0)	571 (26.7)			
35-44	398 (21.3)	456 (21.3)			
45-54	294 (15.7)	422 (19.7)			
55-65	225 (12.0)	345 (16.1)			
Educational Level					
Illiterate	120 (6.4)	102 (4.8)	66.7	<0.01	0.13
Primary	588 (31.5)	833 (38.9)			
Secondary	335 (17.9)	276 (12.9)			
High School	541 (29.0)	491 (22.9)			
University	285 (15.2)	440 (20.5)			
Marital Status					
Married	1232 (65.9)	1706 (79.6)	98.0	<0.01	0.15
Single	528 (28.3)	346 (16.2)			
Divorced	109 (5.8)	90 (4.2)			

*Age categories were based on the age at the baseline assessment.

Table 2. The Associations between the Risk of Incident Clinical Psychosis during Follow-up and Alcohol-Cannabis Use, Forensic Events, Stressful Events

	No Psychosis Endorsement[a] (n:1691)	Incident Clinical Psychosis (n:27)	Univariate Model	Multivariate Model[b]
	n (%)	n (%)	OR (95% CI)	OR (95% CI)
Heavy Drinking (Alcohol)				
No for the last six years	1214 (71.8)	12 (44.5)	1 (ref)	1 (ref)
Present for the last six years	477 (28.2)	15 (55.5)	3.1 (1.5- 6.8)	4.8 (1.8-12.6)
Cannabis Use (at least five times)				
No for the last six years	1666 (98.5)	21 (77.8)	1 (ref)	1 (ref)
Present for the last six years	25 (1.5)	6 (22.2)	19.0 (7.1-51.2)	24.5 (5.4-57.2)
Forensic Events for the Last Six Years				
No	1571 (92.9)	22 (81.5)	1 (ref)	1 (ref)
Present	120 (7.1)	5 (18.5)	3.0 (1.1-8.0)	3.1 (1.1-8.4)
At Least Three Stressful Events for the Last Six Years				
No	1401 (82.8)	10 (37.0)	1 (ref)	1 (ref)
Present	290 (17.2)	17 (63.0)	8.2 (3.7-18.1)	7.3 (3.3- 16.3)
	Mean (SD)	Mean (SD)	β (95% CI)	β^b (95% CI)
The Number of Stressful Events Exposed for the Last Six Years	1.4 (1.3)	3.3 (1.8)	0.7 (0.5-0.9)	0.7 (0.5-0.9)

[a]No 'yes' responses to any psychosis screening questions at the follow-up assessment
[b]Adjusted for age, sex, educational level and social insurance. Significant associations were marked with bold. OR: Odds Ratio CI: Confidence Interval

Table 3. The Associations between the Number of Environmental Risk Factors Exposed and the Risk of Incident Clinical Psychosis during Follow-up

	No Clinical Psychosis	Incident Clinical Psychosis	Univariate Model	Multivariate Model[a]
Environmental Risk[b]	**n (%)**	**n (%)**	**OR (95% CI)**	**OR (95% CI)**
0 risk factor	1147(99.5)	6 (0.52)	ref	ref
1 risk factor	483 (98.3)	8 (1.63)	3.3 (1.1-9.1)	5.5 (1.7-17.6)
2 risk factors	61 (82.4)	13 (17.6)	40.7 (15.0-110.8)	61.9 (20.1-191.3)
Additive impact[c]			12.9 (5.1-32.3)	11.2 (4.3-29.3)

[a]Adjusted for age, sex, educational level and social insurance.
[b]Number or risk factors exposed within the three risk factors evaluated (heavy drinking, cannabis use and at least three stressful events)
[c]Comparison of the group exposed to 1 risk factor with the group exposed to 2risk factors in terms of the risk of incident clinical psychosis
Significant associations were marked with bold. OR: Odds Ratio CI: Confidence Interval

($OR_{adjusted}$=4.8, 95%CI: 1.8-12.6). Furthermore, the risk of incident clinical psychosis gradually increased with increased frequency of monthly consumption of alcohol (r: 0.29, p<0,001).

Forensic event history was significantly associated with the risk of incident clinical psychosis during follow-up ($OR_{adjusted}$=3.1, 95%CI: 1.1-8.4). Similarly, the association was significant with exposure to at least three stressful events ($OR_{adjusted}$= 7.3, 95%CI: 3.3-16.3). Furthermore, the risk of incident clinical psychosis gradually increased with the increasing number of stressful events (β: 0.7, 95%CI: 0.5-0.9).

The Effect of Coexistence of Risk Factors

The associations between the number of environmental risk factors exposed to and the risk of incident clinical psychosis during the follow-up period are presented in Table 3. Results showed increasing risk with the increased exposure to risk factors. The rate of incident clinical psychosis during the follow-up period was 0.5% in participants reporting none of the three risk factors (heavy drinking, cannabis use and ≥3 stressful events). The rate was 1.6% in participants reporting one of these risk factors and 17.6% in participants reporting two. In other words, the risk of incident clinical psychosis was approximately 3 times higher in participants reporting one of the risk factors and 40 times higher in participants reporting two of the risk factors. In comparison to participants with a single risk factor, the risk of incident clinical psychosis was 11 times higher for participants displaying two of the risk factors ($OR_{adjusted}$=11.2, 95%CI: 4.3-29.3).

DISCUSSION

In this study, the associations between heavy drinking, cannabis use, forensic events, stressful events and the risk of incident clinical psychosis was investigated in a prospective follow-up of a representative community-based population. Results showed significantly increased risk with the existence of each of these environmental factors. Furthermore, the risk was significantly higher in cases where these factors coexisted in comparison with the existence of a single risk factor.

Alcohol and Cannabis Use

The results showed significant associations between heavy drinking and incident clinical psychosis during the follow-up period. Furthermore, the risk of incident clinical psychosis significantly increased with the increasing frequency of monthly alcohol use. Besides many environmental risk factors (advanced age of the father, urbanicity, antenatal and perinatal complications, childhood traumas, stressful events, substance abuse etc.), community-based studies have also linked heavy drinking with the risk of clinical psychosis (Kirli and Binbay 2018). In line with our results, a previous community-based study conducted in the city of Izmir showed that alcohol use was associated with a five times higher risk for psychotic symptoms (Alptekin et al. 2009). Two recent meta-analyses of community-based studies also showed significant associations between psychotic symptoms and alcohol use (van Os et al. 2008, Linscott and van Os 2012). Furthermore, the great proportion of studies showed higher rates of alcohol use in first episode psychosis patients than the general population (Larsen et al. 2006, Addington and Addington 2007, Barnett et al. 2007, Harrison et al. 2008, Turkington et al. 2009, Katz et al. 2016, Tan et al. 2018, Cetty et al. 2019, Thungana et al. 2019). However, there are also conflicting results in this area. For example, a study conducted in Norway reported no difference in alcohol use rates between the first episode psychosis patients and the general population (Lange et al. 2014). Furthermore, a recent meta-analysis reported no significant difference in terms of age of onset of the first episode psychosis between individuals with and without alcohol use disorders (Large et al. 2011).

The association between the first episode psychosis and alcohol (if any) seem to be bidirectional. Increasing duration and intensity of alcohol consumption may increase the sensitivity of mesocorticolimbic dopamine network in the brain. This may increase the severity of positive symptoms (Collip et al. 2007). On the other hand, alcohol may be used for self-medication of anxiety caused by psychotic symptoms (Harris and Edlund 2005). A study investigating the motivations behind alcohol consumption in patients with psychotic disorders highlighted 'relieving distressed

mood' as a foremost reason. However, patients also reported that alcohol use mostly increased their positive psychotic symptoms (Pristach and Smith 1996). There are also other results demonstrating a worsening of positive symptoms in psychosis patients due to alcohol (Tsuang and Lohr 1994). On the other hand, the number of studies investigating the associations between alcohol and psychosis to date is limited. Furthermore, there are significant dissimilarities between different communities in terms of prevalence of alcohol use in patients with psychotic disorders as well as the alcohol consumption patterns (Archie et al. 2007, Huang et al. 2009, Eberhard et al. 2015, Kumar et al. 2015). Therefore, further research elucidating the associations between alcohol and psychosis in different parts of the world is needed in order to draw more precise conclusions.

The results of this study showed strong associations between cannabis use and the risk of incident clinical psychosis during follow-up. Furthermore, the risk gradually increased with increased frequency of monthly cannabis use. To date, the associations between cannabis use and psychosis have been shown by a substantial number of longitudinal community-based studies (Moore et al. 2007). Similarly, in line with our results, significant associations between the monthly consumption of cannabis and the risk of psychosis were revealed in previously-conducted studies (Kraan et al. 2015, Kelley et al. 2016). Furthermore, almost all of the first episode psychosis studies showed higher rates of cannabis use in patients compared with the controls (Ortiz-Medina et al. 2018). In connection with this, the cannabis use rate of first episode psychosis patients have been recently investigated in a multicentre study with the participation of 10 European centres and a Brazilian centre. This study reported different rates from different centres ranging from 11% to 51%. The rate of our case group (22%) was similar to the rates of other centres in the Mediterranean region (Barcelona 18.9%, Madrid 21.2%, Palermo 17.1%, Bologna 17.1%) (Di Forti et al. 2019). Some previous studies also showed similar rates of cannabis use in first episode patients (Grech et al. 2005, Turkington et al. 2009, Tosato et al. 2013, Lange et al. 2014). However, two recent meta-analyses showed higher rates of cannabis use in first episode psychosis patients (28.6% and 33.7%) (Koskinen et al. 2010, Myles et al. 2016). These results suggest that the rates of cannabis use in first episode psychosis patients are different in different parts of the world. Therefore, further community-based studies in different regions are of great importance for the management of preventive mental health strategies.

Some authors have explained the association between cannabis and psychosis by the self-medication hypothesis: Individuals who already have susceptibility to psychosis use cannabis more often due to early symptoms; a pattern which later leads to the significant association between psychosis and cannabis (Mane et al. 2015). Investigating this topic with an experimental design is impossible due to ethical concerns. However, some findings to date suggest a causal association between cannabis and psychosis (Stefanis et al. 2004, Henquet et al. 2005). First, the duration between the onset of cannabis use and the emergence of first episode psychosis (5 years in average) was reported to be much longer than the average duration of untreated psychosis (Burns 2013). Second, positive symptoms in individuals who continue to use cannabis after the first episode psychosis were reported to be more severe during follow-up than those who stop using cannabis (Seddon et al. 2016). Furthermore, first episode psychosis was reported to emerge 2.7 years earlier in average in individuals using cannabis (Large et al. 2011). Similarly, neurobiology studies also found some evidence suggesting causality (Shrivastava et al. 2014). Finally, the incidence of psychosis was reported to be higher in cities where the prevalence of cannabis use was higher (Di Forti et al. 2019). Our results in combination with the previous results suggest that cannabis is one of the most important preventable factors in the aetiology of psychosis. Recent studies have shown an uptrend in the prevalence of cannabis use in Turkey (Öğel 2005, Kotan et al. 2018). These results highlight that interventions targeting cannabis use should be planned within the preventive mental health policies for psychosis.

Stressful Events and Forensic Events

The results of this study showed a significant increase in the risk of incident clinical psychosis with the increasing number of stressful events exposed during follow-up. Previous results also suggested that recent stressful events were precipitating factors for psychosis (Lataster et al. 2012, Morgan et al. 2020). Diathesis-stress model proposes that clinical psychosis emerges when stress exceeds the tolerance level (Nuechterlein and Dawson 1984). In line with this model, the results of this study suggest that different stressful events had a cumulative effect on development of psychosis. Plausibly, stressful events lead to a gradual sensitization of the systems related to susceptibility to psychosis (Corcoran et al. 2003, Cullen et al. 2018). However, assuming causality, recent stressful events may only explain less than half of the variation of the risk of clinical psychosis (Ventura et al. 1989, Hogarty and Ulrich 1998). These results suggest that sensitivity pattern of some individuals against stressful events might have their particularities (Lataster et al. 2012).

The results of this study showed that the risk of clinical psychosis was significantly higher in individuals with a history of a forensic event during the follow-up period. As far as we know, the association with forensic events was investigated in a longitudinal design for the first time. This association may be interpreted from various perspectives. First, the psychosocial stress exposed to during the forensic event might itself lead to

the sensitization of systems related to psychosis-susceptibility. Another point of view is the hypothesis of 'common vulnerability' according to which adverse events exposed to prior to a forensic event might both lead to the forensic event and to the course of psychosis (Gunter et al. 2012). On the other hand, the positive symptoms as well as the cognitive deterioration associated with the natural course of psychosis might lead to a greater risk of committing or being exposed to a crime. In line with this hypothesis, individuals at ultra-high risk for psychosis were reported to have associations with greater number of forensic events (Purcell et al. 2015).

The Effect of Coexistence of Risk Factors

The results of this study show that the risk of incident clinical psychosis increased substantially upon exposure to multiple environmental risk factors. This finding is consistent with previous results suggesting an additive impact of multiple environmental risk factors on risk of psychosis (Cougnard et al. 2007, Guloksuz et al. 2015, Pries et al. 2018). In the light of these results, recent studies have been published to estimate an exposome score for psychosis as a measure of cumulative environmental risk (Morgan et al. 2018, Pries et al. 2019). This approach, despite its current limitations, is promising in terms of evaluation of the risk of psychosis more accurately as well as to plan preventive interventions in the near future (Fusar-Poli et al. 2017). Studies evaluating genetic liability in combination with the exposome score may provide important insights in the area of psychosis research.

The Strengths and the Limitations of the Study

This study was conducted in a relatively large representative general population sample with a longitudinal design. The variables were assessed using a fully-structured interview form. The dependent variable (incident clinical psychosis) was assessed via interviews performed by physicians instead of the assessment of merely self-reported information. The prospective follow-up of a community-based sample provided the opportunity to detect cases of incident clinical psychosis during follow-up. Furthermore, this design enabled the study of single impact of risk factors as well as the combined impact of multiple factors at different time points.

In addition to the above-mentioned strengths, the following limitations of the study should also be noted. First is the attrition of a part of the sample during the follow-up period and a potential sampling bias. The attrition rate of this study is similar to previous studies with of a similar design (Dominguez et al. 2009, Zammit et al. 2013). The response rate of men, younger age groups, non-married individuals and high school graduates is relatively low. These subgroups had higher attrition rates also in previous studies of a similar design (Graaf et al. 2000, Dominguez et al. 2013). Furthermore, younger age and being non-married might be associated with the risk of incident clinical psychosis (Linscott and van Os 2012). However, the probability of differential distribution of these subgroups per investigated risk factors (stressful events, alcohol and cannabis use) is low. Furthermore, the analysis of the differences between respondents and the non-respondents in terms of sex, age, educational level and marital status showed very small effect sizes (Cramer's V from 0.04 to 0.15). Second, the duration between the baseline and the follow-up assessments is relatively long. This long period might have limited the examination of the details of the psychotic course. On the other hand, the same lengthy period might also have prevented the disturbance of the natural course, which can be considered an advantage. However, it might also have led to recall bias. Furthermore, the short term variability of the symptoms could not be investigated (Schlenger et al. 2015). Third, the screening interviews were conducted by lay-interviewers, who were not physicians. Any screening form may lead to false positives or false negatives (van Os et al. 2008, Nuevo et al. 2012). Although data was collected via a fully-structured interview form, the interviews were performed by multiple interviewers, which was also a limitation; to overcome which certain methodologies were employed. The interviewers were selected among medical students or psychologists. Immediate supervisions for the lay-interviewers continued during all phases of the study. The quality of the interviews was systematically checked and interviews with low quality were repeated. Thus, 40% of the screening interviews were checked by physicians during face-to-face interviews or on telephone. Furthermore, the dependent variable '*incident clinical psychosis*' was coded with reliance on physician discretion to minimise the risk of false positivity. Then, different information sources besides lay-interviews were used to code the dependent variable (help-seeking behaviour, attendance to outpatient clinics, history of the diagnoses and the medication, hospitalization etc.). Therefore, the risk of false negative was also minimised. The fourth limitation was the potential modification of the results by treatments during follow-up. Although data was collected on help-seeking behaviour as well as treatments, a potential impact of treatments on results could not be completely ruled out. The fifth was the non-representation of those who were hospitalized or imprisoned due to the sampling method (household visits). As both groups are relatedly small, this might have had a small impact on the results. The sixth was the small number of individuals with incident clinical psychosis during follow-up (n: 27). This led to wide confidence intervals in the analyses investigating associations with environmental risk factors. Therefore, these results need replication. Finally, data on alcohol and cannabis use was based on self-reported information and no tests were carried out on biological material (urine, blood, hair etc.). However, biological tests can only provide information on short-term

substance use (Taylor et al. 2017). Furthermore, studies comparing biological tests with self-reported information on cannabis use showed that these two data collection methods were highly compatible (Freeman et al. 2014, Curran et al. 2018).

CONCLUSION

This study investigated the risk factors for clinical psychosis with a longitudinal design in a representative community-based sample. The results showed that heavy drinking, cannabis use, recent stressful events and forensic events were associated with the risk of incident clinical psychosis. The association was particularly strong with cannabis use. Furthermore, the substantial increase in the risk of clinical psychosis in case of coexistence of environmental risk factors was noteworthy. Interventions for these modifiable risk factors should be planned as part of preventive/risk-reducing mental health strategies.

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