



Cannabis use is associated with 3 years earlier onset of schizophrenia spectrum disorder in a naturalistic, multi-site sample (N = 1119)

Siri Helle ^{a,*}, Petter Andreas Ringen ^{b,c}, Ingrid Melle ^{b,c}, Tor-Ketil Larsen ^{d,e}, Rolf Gjestad ^a, Erik Johnsen ^{a,e}, Trine Vik Lagerberg ^{b,c}, Ole A. Andreassen ^{b,c}, Rune Andreas Kroken ^{a,e}, Inge Joa ^{d,f}, Wenche ten Velden Hegelstad ^d, Else-Marie Løberg ^{a,g}

^a Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

^b Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

^c NORMENT K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Norway

^d Division of Psychiatry, Centre for Clinical Research in Psychosis, Stavanger University Hospital, Norway

^e Department of Clinical Medicine, University of Bergen, Norway

^f Network for Medical Sciences, Faculty of Social Sciences, University of Stavanger, Norway

^g Department of Clinical Psychology, University of Bergen, Norway

ARTICLE INFO

Article history:

Received 17 March 2015

Received in revised form 22 November 2015

Accepted 27 November 2015

Available online 9 December 2015

Keywords:

Schizophrenia

Non-affective psychosis

Age at onset

Cannabis

Substance

Substance use

ABSTRACT

Background: Patients with schizophrenia spectrum disorders and substance use may have an earlier onset of illness compared to those without substance use. Most previous studies have, however, too small samples to control for confounding variables and the effect of specific types of substances. The present study aimed to examine the relationship between substance use and age at onset, in addition to the influence of possible confounders and specific substances, in a large and heterogeneous multisite sample of patients with schizophrenia spectrum disorders.

Methods: The patients (N = 1119) were recruited from catchment areas in Oslo, Stavanger and Bergen, Norway, diagnosed according to DSM-IV and screened for substance use history. Linear regression analysis was used to examine the relationship between substance use and age at onset of illness.

Results: Patients with substance use (n = 627) had about 3 years earlier age at onset (23.0 years; SD 7.1) than the abstinent group (n = 492; 25.9 years; SD 9.7). Only cannabis use was statistically significantly related to earlier age at onset. Gender or family history of psychosis did not influence the results.

Conclusion: Cannabis use is associated with 3 years earlier onset of psychosis.

© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Patients with schizophrenia spectrum disorders and substance use seem to have an earlier age at onset of their illness than patients without substance use. This has most consistently been shown in relation to cannabis use (Barnes et al., 2006; Barnett et al., 2007; Bhavsar, 2015; Donoghue et al., 2014; Large et al., 2011; Mane et al., 2015; Myles et al., 2012; Power et al., 2013; Tosato et al., 2013) and to some degree to use of stimulants such as amphetamines, cocaine and ecstasy (Power et al., 2013; van der Meer et al., 2014). Most studies have, however, too small samples to investigate the effect of specific types of substances. Large et al. (2011) tried to examine the effects of specific substances by mean of a meta-analysis; a 2 and 2.7 years earlier age at onset was reported for unspecified substance use and cannabis use, respectively. The effect of cannabis was emphasized by the authors, but

also the need for large scale samples to analyze individual data (Large et al., 2011).

Moreover, there may be characteristics that are associated with both substance use and age at onset that confound this relationship. An association between earlier age at onset and a family history of psychosis has been reported (McInnis et al., 1999), and a higher familial vulnerability, i.e. having a higher distribution of relatives with psychosis, in substance using patients has been suggested (McGuire et al., 1995). Gender might also be a confounder, as males have both earlier age at onset and more substance use (Abel et al., 2010). In conclusion, there is still considerable ambiguity concerning the association between substance use and age at onset.

The main aims of this study were to: 1) examine the relationship between substance use and age at onset, in addition to the influence of possible confounders, in schizophrenia spectrum disorders, 2) examine the effect of specific substance use, such as cannabis, stimulants, cocaine, opiates and hallucinogens, on this relationship. In order to achieve this, a large and heterogeneous multisite sample of patients with schizophrenia spectrum disorders was included.

* Corresponding author at: Division of Psychiatry, Haukeland University Hospital, Sandviksleitet 1, N-5035 Bergen, Norway.

E-mail address: siri.helle@helse-bergen.no (S. Helle).

2. Methods

2.1. Overview

Data from three different clinical research sites in Norway was used: the Thematically Organized Psychosis Study (TOP study) Oslo area ($n = 873$), 2000–2012; Early Treatment and Intervention in Psychosis study (TIPS-II study), Rogaland area ($n = 185$), 2001–2012; and the Bergen Psychosis Project 2, (BP2 study, 2012–2013; Neurocognition of Schizophrenia (NOS study, 2000–2002)), Bergen area ($n = 71$). Inclusion criteria were: a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder and psychosis not otherwise specified, living in the respective catchment areas and age 18–65 years. Patients were excluded from the study if they had a history of moderate/severe head injury, neurological disorder, or if they did not speak a Scandinavian language (Joa et al., 2008; Lagerberg et al., 2011; Løberg and Hugdahl, 2009).

Patients in all of the three samples gave informed consent and the respective projects were approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

2.2. Clinical assessments

Diagnoses were evaluated by means of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995), modules A–E, administered by trained clinical psychologists and psychiatrists. The inter-rater reliability of diagnosis has been reported to be high in both the TOP, Kappa value of 0.77 (Ringen et al., 2008) and the TIPS-II study, Kappa value of 0.9 (Weibell et al., 2013). There was no measure of reliability for diagnosis from the Bergen Psychosis Project 2. All the raters in the TOP and TIPS-II study completed training courses in SCID assessments and there has been a cooperation between the two sites with regard to inter-rater reliability and validity of clinical measures (Friis et al., 2003). The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989) was used to rate psychotic symptoms at baseline in the respective projects. Age at onset was defined as the first psychotic episode/and or first time the patient had a clinically significant score (≥ 4) on one or more of the following items from the Positive and Negative Syndrome Scale: Delusions, Hallucinatory behavior, Grandiosity, Suspiciousness/Persecution, or Unusual thought content (Friis et al., 2003), with a duration of at least one week. The accuracy of the estimation of age at onset was depending on the accessible information in each case. When age at onset of psychotic symptoms was missing, which was the case for 18 patients, age of the first consultation at psychiatric services due to psychosis was used as a proxy for age at onset.

The Global Assessment of Functioning scale (GAF), split version, was used to assess the general level of symptoms and functioning at baseline (Pedersen et al., 2007). Family history of schizophrenia or bipolar disorder among first degree relatives was obtained through patient interviews (i.e. mother, father, sisters and brothers). Patients having at least one first-degree relative with schizophrenia or bipolar disorder were defined as having a family history of psychosis. Age at initiation of antipsychotic medication use was registered by examining journals and interviewing patients.

Substance use was documented through interviews regarding lifetime use of substances, urine samples, and use of the Clinical Drug Use Scale (DUS) and the Clinical Alcohol Use Scale (AUS) (Drake et al., 1996; Drake et al., 1990). Substance use disorders were diagnosed using the SCID-E module (First et al., 1995). All accessible information in each case was examined to avoid false negative substance users. Patients' severity of alcohol use was rated on a 5-point scale (1 = abstinence, 2 = use without impairment, 3 = abuse, 4 = dependence, 5 = severe dependence) by use of AUS. The equivalent DUS rating scale, was administrated for estimating severity of substance use (Drake et al., 1996). The TIPS-II study ($n = 216$) only recorded use of substances the last 6 months before inclusion and no lifetime substance

use. Patients were split into two groups; Substance and Abstinent, based on whether or not they had ever used substances including cannabis, amphetamines, cocaine, hallucinogens and opiates. Specifically, groups were defined on the fulfillment or not of at least one of the following criteria: 1) a score of 2 or more on the Clinical Drug Use Scale 2) a DSM-IV diagnosis of substance use, abuse or dependence 3) lifetime registration of substance use and 4) positive results on urine tests for substances. Thus, the Abstinent group had never used cannabis or any other illicit substance that were recorded.

2.3. Statistical analyses

All statistical analyses were performed using SPSS software, version 21.0 (IBM). Categorical variables are presented in percentage and number. Descriptive continuous variables are presented by mean and standard deviation in the two groups. Independent t-tests and chi-square analyses were used to examine differences in variables in the two groups. Regression analyses were performed with age at onset as the dependent variable and use of substances as the independent (predictor) variable. Analyses were run separately in the respective samples to examine if the relationship between the variable, age at onset and use of substances, were the same before data were merged into one dataset. These initial analyses confirmed an association between age at onset and use of substances in all samples, in the direction that substance use was associated with earlier age at onset. The data sets were then merged and the regression analyses performed for the merged sample. Preliminary analyses were conducted in the whole sample to ensure that the assumptions of linearity, multi-collinearity and homoscedasticity were met. The skewness of 1.110, and kurtosis 1.701 of the age at onset variable, indicate that the normality assumption was not violated (Curran et al., 1996). There were missing in the following variables: Family history of psychosis (113); Education, years (25); Duration of illness, years (68); Age when started using anti-psychotic medication (186); Positive sub-scale (7); Negative sub-scale (9); General psychopathology sub-scale (13); PANSS Total (19); GAF function score (2); GAF symptom score (3); CDUS (140); CAUS (142). A stepwise regression analysis was performed where age at onset was the dependent variable and the following independent variables were entered in a specified order: gender, use of alcohol (Clinical Alcohol Use Scale), use of certain types of substances, such as cannabis, stimulants, cocaine, opiates, and hallucinogens, and the interaction term between specific substances and gender. Pearson correlations (Pearson's r) were used to assess bivariate associations between the predictor variables. Listwise deletion in the regression analysis reduced the sample size when multiple variables with missing cases were included. Specifically, a one way between-groups analysis of covariance was used to examine whether the effect of specific substances on age at onset remained significant after adjusting for a family history of psychosis.

3. Results

3.1. Groups comparisons on demographic and clinical characteristics

Patients in the two groups were compared on all demographic and clinical characteristics (Table 1). There were more males in the Substance group; 67.8%, compared to the Abstinent group, 53.5%. A higher proportion of the Abstinent group was diagnosed with schizoaffective disorder; 15.4%, compared to the Substance group, 10.6%, and there was a higher proportion of the Substance group, which was diagnosed with psychotic disorder not otherwise specified; 19.9%, compared to the Abstinent group, 12.0%. In addition, the Abstinent group patients were older, had a higher mean total years of education, a longer mean duration of illness, a higher mean age of initiating antipsychotic treatment, a lower score on PANSS General Psychopathology scale and a higher score on GAF functioning (see Table 1 for details). The Substance

Table 1
Demographic and clinical characteristics of abstinent and substance using patients.

	Abstinent group n (%)	Substance group n (%)	P-value
Group distribution	492 (44.0%)	627 (56.0%)	
Male	263 (53.5%)	425 (67.8%)	.000**
Schizophrenia	273 (55.6%)	361 (57.6%)	.028 ^a
Schizoaffective	76 (15.4%)	67 (10.6%)	
Delusional disorder	38 (7.7%)	32 (5.1%)	.001 ^{a,b}
Psychosis not otherwise specified	59 (12.0%)	125 (19.9%)	
Schizophreniform disorder	33 (6.7%)	23 (3.7%)	.098 ^c
Brief psychosis	13 (2.6%)	19 (3.0%)	
Family history of psychosis	91 (20.7%)	101 (17.3%)	.259
	Mean (SD)	Mean (SD)	
Age	32.3 (11.2)	28.3 (8.3)	.000**
Education (years)	12.9 (3.0)	12.0 (2.6)	.000**
Age at onset of psychotic symptoms	25.9 (9.7)	23.0 (7.1)	.000**
Duration of illness, years	6.4 (7.9)	5.0 (6.2)	.001 ^e
Age when started using ap. ^d	28.0 (9.4)	25.1 (7.0)	.000**
PANSS ^e			
Positive sub-scale	15.6 (5.5)	15.9 (5.3)	.518
Negative sub-scale	15.1 (6.3)	15.6 (6.4)	.163
Gen. psychopath. sub-scale ^f	31.5 (8.3)	32.5 (8.2)	.042 ^e
Total	62.4 (16.4)	64.2 (16.4)	.086
GAF function score ^g	44.2 (11.3)	42.0 (11.3)	.002 ^e
GAF symptom score	40.8 (11.7)	40.2 (11.6)	.441
CDUS ^h	1.0 (.0)	2.0 (1.1)	.000**
CAUS ⁱ	1.7 (.6)	2.1 (.7)	.000**

* Significant at the .05 level.

** Significant at the .001 level.

^a P-value for comparison of schizophrenia plus schizoaffective disorder.

^b P-value for comparison of delusional plus psychosis not otherwise specified.

^c P-value for comparison of schizophreniform disorder plus brief psychosis.

^d Age when started using anti-psychotic medication.

^e PANSS = Positive and Negative Syndrome Scale.

^f Gen. psychopath. sub-scale = General Psychopathology sub-scale.

^g GAF = the Global Assessment of Functioning.

^h CDUS = Clinical Drug Use Scale.

ⁱ CAUS = Clinical Alcohol Use Scale.

group had higher score on the Clinical Drug Use Scale and Alcohol Use Scale.

3.2. The association between age at onset and specific types of substances, gender and family history

Bivariate analysis showed that the Substance group had an earlier mean age at onset ($M = 23.0$; $SD 7.1$) compared to the Abstinent group, 25.9 ($SD 9.7$). Thus, the patients with substance use had a 2.9 year earlier onset than the patients without substance use.

The result from the stepwise regression analysis including the variables gender, alcohol and specific substances is shown in Table 2. Of note, neither gender, use of alcohol nor the interaction term between gender and the specific substances were significantly associated to age

Table 2
Results of stepwise regression analysis, including gender, alcohol use and illicit substances ($n = 977$).

	b	SE-b	Beta	t	P value	95% CI of B	
						Lower	Upper
Constant	27.014	1.178		22.938	.000**	24.703	29.325
Gender	-.555	.576	-.031	-.964	.335	-1.686	.575
Alcohol	-.171	.419	-.013	-.409	.683	-.994	.651
Cannabis	-2.648	.683	-.150	-3.876	.000**	-3.989	-1.307
Amphetamines	.081	.921	.004	.088	.930	-1.726	1.889
Cocaine	-.831	1.029	-.038	-.807	.420	-2.850	1.188
Hallucinogens	.385	1.037	.017	.371	.711	-1.650	2.419
Opiates	-1.045	1.055	-.036	-.991	.322	-3.115	1.025

The dependent variable was age at onset. $R^2 = .032$, Adjusted $R^2 = .025$.

** Significant at the .001 level.

at onset, thus these variables were removed. The re-estimated model with the specific substances explained 2.9% of the variance in age at onset, $F(5, 1113) = 6.66$, $P = 0.001$. Only cannabis, of all investigated substances of use, was significantly related to age at onset ($\beta = -.16$, $P < 0.001$). See Table 3 for bivariate correlations between the predictor variables. Of note, there were moderate positive associations between use of cannabis and use of amphetamines, cocaine and hallucinogens, whilst the association between cannabis and opiate use was weak.

The effect of cannabis remained significant, $F(1, 1003) = 31.66$, $P < 0.001$, and there was no main effect of family history of psychosis on age at onset ($F(1, 1003) = 0.30$, $P = 0.862$). Also, there was no interaction between cannabis use and family history of psychosis.

4. Discussion

In the present study, patients with a schizophrenia spectrum psychosis and substance use had almost 3 years earlier onset of psychotic symptoms, compared to patients without substance use. Earlier age at onset was specifically related to cannabis use and not to any other substance use (including alcohol use), nor to gender or having a family history of psychosis. The results from the present study is in line with other studies reporting approximately 3 years earlier age at onset of positive psychotic symptoms in patients with schizophrenia spectrum disorder that have been using cannabis (Di Forti et al., 2013; Large et al., 2011). What is new is that this study documents earlier age at onset in patients with substance use in a relative large multi-site sample that allows for the investigation of difference substances and for the influence of possible confounders.

Cannabis was used by 9 of 10 of the substance using patients. Of note, there were moderately strong positive correlations between the use of cannabis and amphetamines, cocaine and hallucinogens, confirming that these are somehow associated. However, each specific substance could explain its own unique proportion of the variance in the model, thus the specific substances are regarded as acceptable robust predictors. Although, the use of stimulants has previously been shown to be significantly related to age at onset (Power et al., 2013; van der Meer et al., 2014), this was not replicated in the present study.

Earlier age at onset has also been reported in men compared to women (Abel et al., 2010). It has been suggested that cannabis use forward age at onset in women, reducing the gender differences (Allegri et al., 2013; Donoghue et al., 2014). However, earlier age at onset was not associated with female or male gender in the present study indicating that the association between cannabis use and onset age was the same in both genders.

In the present study there were no differences in regard to the distribution of family history of psychosis in the substance using and abstinent patients groups. This has also been found in other studies (Boydell et al., 2007; Proal et al., 2014), and indicates that the level of familial vulnerability may be the same in both groups. Most patients have started using cannabis before psychosis breakthrough (Goldberger et al., 2010; Myles et al., 2015; Rabinowitz et al., 1998; Sevy et al., 2010; Stefanis et al., 2013), but developmental processes related to psychosis itself can theoretically influence the disposition to take substances, and this is hard to test empirically. This relationship is further complicated by shared vulnerability for substance use and psychosis (Hartz et al., 2014).

Some limitations of the present study should be taken into consideration. Information on whether substance use preceded or followed the age at onset is relevant when attempting to establish a causal relationship between cannabis use and onset of psychosis. Lower education level in the substance users in the present study could indicate lower economic status, which again could be linked to cannabis use. The relationship between and substance use and economic status may be bidirectional (Sevy et al., 2010). In 18 cases "date of first contact with psychiatric services for a psychotic disorder" was used as a proxy for age at

Table 3

Bivariate correlations (Pearson's R) between sociodemographic factors, substance type and age at onset in 977 patients with non-affective psychosis.

	Age at onset	Gender	Alcohol	Cannabis	Amphetamines	Cocaine	Hallucinogens	Opiates
Age at onset	1.000	-.010	-.059	-.169	-.104	-.113	-.089	-.084
Gender		1.000		-.108	-.140	-.101	-.124	-.093
Alcohol			1.000	.242	.219	.245	.224	.146
Cannabis				1.000	.533	.490	.454	.277
Amphetamines					1.000	.650	.623	.423
Cocaine						1.000	.658	.425
Hallucinogens							1.000	.441
Opiates								1.000

Note. Only significant associations are shown (P values < .05).

onset, this is not an accurate measure of the debut of psychotic symptoms due to treatment-delay (Breitborde et al., 2009). This study lacks information concerning the duration of the prodromal period, which could have shed more light on the relationship between illness processes in regard to start of cannabis use. Furthermore, information on family history of psychosis was based on patient report and the reliability of this method has been questioned (Roy et al., 1996). Another limitation is that a clinical rating of the alcohol use the last 6 months were used as a predictor variable in the regression analysis, in this case, a lifetime measure of alcohol use would have been a more valid measure for the purpose of the present study.

The finding from the present study emphasizes cannabis as an environmental factor associated with a 3 years earlier age at onset of psychotic symptoms. No other illegal substance was related to earlier age at onset, suggesting a specific effect of cannabis and a need for understanding the mechanism behind this relationship.

Contributors

Ingrid Melle and Ole A. Andreassen took part in designing the TOP study and Tor-Ketil Larsen and Inge Joa took part in designing the TIPS-II study. Erik Johnsen and Rune Kroken participated in designing BP2. Else-Marie Løberg participated in designing BP2 and NOS study. Trine Vik Lagerberg and Petter Andreas Ringen designed the substance use instrument and contributed to the data collection in the TOP study. Authors Siri Helle and Else-Marie Løberg wrote the first draft of the manuscript. Siri Helle performed the statistical analysis in the manuscript after feedback from Rolf Gjestad. All authors have contributed to and have approved the final manuscript.

Role of funding source

The funding source had no involvement in the authors' work.

Conflict of interest

Ole A. Andreassen has received speakers' honorarium from Lundbeck, Otsuka and Lilly, Erik Johnsen has received honoraria for lectures given in meetings arranged by Bristol-Myers Squibb, Eli Lilly, and AstraZeneca, has consulted for Eli Lilly, and have been reimbursed by Eli Lilly and Janssen Cilag for attending conferences. The other authors report no competing interests related to the present work.

Acknowledgments

The authors thank the participants for their contribution to the study. The present study was funded by grants from the Research Council in Norway (No. 217776, 223273, 134088/320, 213727) and South-East Norway Health Authority (No. 2013-123); from Helse-Vest Health Authority (No. 911313, 911368, 911617).

References

- Abel, K.M., Drake, R., Goldstein, J.M., 2010. Sex differences in schizophrenia. *Int. Rev. Psychiatry* 22 (5), 417–428.
- Allegri, F., Belvederi Murri, M., Paparelli, A., Marcacci, T., Braca, M., Menchetti, M., Michetti, R., Berardi, D., Tarricone, I., 2013. Current cannabis use and age of psychosis onset: a gender-mediated relationship? Results from an 8-year FEP incidence study in Bologna. *Psychiatry Res.* 210 (1), 368–370.
- Barnes, T.R., Mutsaers, S.H., Hutton, S.B., Watt, H.C., Joyce, E.M., 2006. Comorbid substance use and age at onset of schizophrenia. *Br. J. Psychiatry* 188, 237–242.
- Barnett, J.H., Werners, U., Secher, S.M., Hill, K.E., Brazil, R., Masson, K., Pernet, D.E., Kirkbride, J.B., Murray, G.K., Bullmore, E.T., Jones, P.B., 2007. Substance use in a population-based clinic sample of people with first-episode psychosis. *Br. J. Psychiatry* 190 (6), 515–520.
- Bhavsar, V., 2015. Environmental factors, including cannabis, are strongly related to the age of onset and morbidity of schizophrenia. *Evid. Based Ment. Health* 18 (3), 84.
- Boydell, J., Dean, K., Dutta, R., Giouroukou, E., Fearon, P., Murray, R., 2007. A comparison of symptoms and family history in schizophrenia with and without prior cannabis use: implications for the concept of cannabis psychosis. *Schizophr. Res.* 93 (1–3), 203–210.
- Breitborde, N.J., Srihari, V.H., Woods, S.W., 2009. Review of the operational definition for first-episode psychosis. *Early Interv. Psychiatry* 3 (4), 259–265.
- Curran, P.J., West, S.G., Finch, J.F., 1996. The robustness of test statistics to nonnormality and specification error in confirmatory factor analysis. *Psychol. Methods* 1 (1), 16–29.
- Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S.A., Marconi, A., La Cascia, C., Reis Marques, T., Pariente, C., Dazzan, P., Mondelli, V., Paparelli, A., Kolliakou, A., Prata, D., Gaughan, F., David, A.S., Morgan, C., Sthal, D., Khondoker, M., Maccabe, J.H., Murray, R.M., 2013. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr. Bull.* 40 (6), 1509–1517.
- Donoghue, K., Doody, G.A., Murray, R.M., Jones, P.B., Morgan, C., Dazzan, P., Hart, J., Mazzoncini, R., Maccabe, J.H., 2014. Cannabis use, gender and age of onset of schizophrenia: data from the AESOP study. *Psychiatry Res.* 215 (3), 528–532.
- Drake, R.E., Mueser, K.T., McHugo, G.J., 1996. Clinical rating scales: Alcohol Use Scale (AUS), Drug Use Scale (DUS), and Substance Abuse Treatment Scale (SATS). In: Sederer, L.L., Dickey, E. (Eds.), *Outcomes Assessment in Clinical Practice*. Williams & Wilkins, Baltimore, pp. 113–116.
- Drake, R.E., Osher, F.C., Noordsy, D.L., Hurlbut, S.C., Teague, G.B., Beaudett, M.S., 1990. Diagnosis of alcohol use disorders in schizophrenia. *Schizophr. Bull.* 16 (1), 57–67.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, G.M., 1995. *Structured Clinical Interview of DSM-IV Axis I Disorders (SCID-I): Patient Edition. Version 2. State Psychiatric Institute, Biometrics Research, NY, New York*.
- Friis, S., Larsen, T.K., Melle, I., Opjordsmoen, S., Johannessen, J.O., Haahr, U., Simonsen, E., Rund, B.R., Vaglum, P., McGlashan, T., 2003. Methodological pitfalls in early detection studies – the NAPE Lecture 2002. *Nordic Association for Psychiatric Epidemiology. Acta Psychiatr. Scand.* 107 (1), 3–9.
- Goldberger, C., Dervaux, A., Gourion, D., Bourdel, M.C., Loo, H., Laqueille, X., Krebs, M.O., 2010. Variable individual sensitivity to cannabis in patients with schizophrenia. *Int. J. Neuropsychopharmacol.* 13 (9), 1145–1154.
- Hartz, S.M., Pato, C.N., Medeiros, H., Cavazos-Reh, P., Sobell, J.L., Knowles, J.A., Bierut, L.J., Pato, M.T., for the Genomic Psychiatry Cohort, Consortium, Abbott, C., Azevedo, M.H., Belliveau, R., Bevilacqua, E., Bromet, E.J., Buckley, P.F., Dewan, M.J., Escamilla, M.A., Fanous, A.H., Fochtmann, L.J., Kinkade, R., Kotov, R., Lehrer, D.S., Macciardi, F., Malaspina, D., Marder, S.R., McCarroll, S.A., Moran, J., Morley, C.P., Nicolini, H., Perkins, D.O., Potkin, S.G., Purcell, S.M., Rakofsky, J.J., Rapaport, M.H., Scolnick, E.M., Sklar, B., Sklar, P., Smoller, J.W., Sullivan, P.F., Vitar, A., 2014. Comorbidity of severe psychotic disorders with measures of substance use. *JAMA Psychiatry* 71 (3), 248–254.
- Joa, I., Johannessen, J.O., Auestad, B., Friis, S., McGlashan, T., Melle, I., Opjordsmoen, S., Simonsen, E., Vaglum, P., Larsen, T.K., 2008. The key to reducing duration of untreated first psychosis: information campaigns. *Schizophr. Bull.* 34 (3), 466–472.
- Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1989. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br. J. Psychiatry Suppl.* 7, 59–67.
- Lagerberg, T.V., Sundet, K., Aminoff, S.R., Berg, A.O., Ringen, P.A., Andreassen, O.A., Melle, I., 2011. Excessive cannabis use is associated with earlier age at onset in bipolar disorder. *Eur. Arch. Psychiatry Clin. Neurosci.* 261 (6), 397–405.
- Large, M., Sharma, S., Compton, M.T., Slade, T., Nielssen, O., 2011. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch. Gen. Psychiatry* 68 (6), 555–561 <http://www.ncbi.nlm.nih.gov/pubmed/21300939>.
- Løberg, E.M., Hugdahl, K., 2009. Cannabis use and cognition in schizophrenia. *Front. Hum. Neurosci.* 3, 53.
- Mane, A., Fernandez-Exposito, M., Berge, D., Gomez-Perez, L., Sabate, A., Toll, A., Diaz, L., Diez-Aja, C., Perez, V., 2015. Relationship between cannabis and psychosis: reasons for use and associated clinical variables. *Psychiatry Res.* 229 (1–2), 70–74.
- McGuire, P.K., Jones, P., Harvey, I., Williams, M., McGuffin, P., Murray, R.M., 1995. Morbid risk of schizophrenia for relatives of patients with cannabis-associated psychosis. *Schizophr. Res.* 15 (3), 277–281.
- McInnis, M.G., McMahon, F.J., Crow, T., Ross, C.A., DeLisi, L.E., 1999. Anticipation in schizophrenia: a review and reconsideration. *Am. J. Med. Genet.* 88 (6), 686–693.
- Myles, H., Myles, N., Large, M., 2015. Cannabis use in first episode psychosis: meta-analysis of prevalence, and the time course of initiation and continued use. *Aust. N. Z. J. Psychiatry*. <http://dx.doi.org/10.1177/000486741559846>.
- Myles, N., Newall, H., Nielssen, O., Large, M., 2012. The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: meta-analysis of possible confounding factors. *Curr. Pharm. Des.* 18 (32), 5055–5069.

- Pedersen, G., Hagtvet, K.A., Karterud, S., 2007. Generalizability studies of the Global Assessment of Functioning—split version. *Compr. Psychiatry* 48 (1), 88–94.
- Power, B.D., Dragovic, M., Jablensky, A., Stefanis, N.C., 2013. Does accumulating exposure to illicit drugs bring forward the age at onset in schizophrenia? *Aust. N. Z. J. Psychiatry* 47 (1), 51–58.
- Proal, A.C., Fleming, J., Galvez-Buccollini, J.A., Delisi, L.E., 2014. A controlled family study of cannabis users with and without psychosis. *Schizophr. Res.* 152 (1), 283–288.
- Rabinowitz, J., Bromet, E.J., Lavelle, J., Carlson, G., Kovaszny, B., Schwartz, J.E., 1998. Prevalence and severity of substance use disorders and onset of psychosis in first-admission psychotic patients. *Psychol. Med.* 28 (6), 1411–1419.
- Ringen, P.A., Lagerberg, T.V., Birkenaes, A.B., Engn, J., Faerden, A., Jonsdottir, H., Nesvag, R., Friis, S., Opjordsmoen, S., Larsen, F., Melle, I., Andreassen, O.A., 2008. Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. *Psychol. Med.* 38 (9), 1241–1249.
- Roy, M.A., Walsh, D., Kendler, K.S., 1996. Accuracies and inaccuracies of the family history method: a multivariate approach. *Acta Psychiatr. Scand.* 93 (4), 224–234.
- Sevy, S., Robinson, D.G., Napolitano, B., Patel, R.C., Gunduz-Bruce, H., Miller, R., McCormack, J., Lorell, B.S., Kane, J., 2010. Are cannabis use disorders associated with an earlier age at onset of psychosis? A study in first episode schizophrenia. *Schizophr. Res.* 120 (1–3), 101–107.
- Stefanis, N.C., Dragovic, M., Power, B.D., Jablensky, A., Castle, D., Morgan, V.A., 2013. Age at initiation of cannabis use predicts age at onset of psychosis: the 7- to 8-year trend. *Schizophr. Bull.* 39 (2), 251–254.
- Tosato, S., Lasalvia, A., Bonetto, C., Mazzoncini, R., Cristofalo, D., De Santi, K., Bertani, M., Bissoli, S., Lazzarotto, L., Marrella, G., Lamonaca, D., Riolo, R., Gardellin, F., Urbani, A., Tansella, M., Ruggeri, M., Group, P.-V., 2013. The impact of cannabis use on age of onset and clinical characteristics in first-episode psychotic patients. Data from the Psychosis Incident Cohort Outcome Study (PICOS). *J. Psychiatr. Res.* 47 (4), 438–444.
- van der Meer, F.J., Meijer, J.H., Meijer, C.J., van den Brink, W., Velthorst, E., 2014. Cognitive functioning associated with stimulant use in patients with non-affective psychosis, their unaffected siblings and healthy controls. *Psychol. Med.* 44 (9), 1901–1911.
- Weibell, M., Joa, I., Bramness, J., Johannessen, J., McGorry, P., ten Velden Hegelstad, W., Larsen, T.K., 2013. Treated incidence and baseline characteristics of substance induced psychosis in a Norwegian catchment area. *BMC Psychiatry* 13 (1), 319.