Title: Age at the time of onset of psychosis: A marker of specific needs rather than a determinant of outcome?
Authors: Golay P, Alameda L, Mebdouhi N, Baumann P, Ferrari C, Solida A, Progin P, Elowe J, Conus P
Journal: European psychiatry : the journal of the Association of European Psychiatrists
Year: 2017 Jun 21
Volume: 45
Pages: 20-26
DOI: 10.1016/j.eurpsy.2017.06.002

Age at the time of onset of psychosis: a marker of specific needs rather than a determinant of outcome?

Philippe Golay[ab], Luis Alameda[acd], Nadir Mebdouhi[a], Philipp Baumann[ac], Carina Ferrari[a], Alessandra Solida[a], Pierre Progin[a], Julien Elowe[e], Philippe Conus[a]

a. Service of General Psychiatry, Treatment and Early Intervention in Psychosis Program (TIPP-Lausanne), Lausanne University Hospital (CHUV), Switzerland.

b. Service of Community Psychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), Switzerland.

c. Unit for Research in Schizophrenia, Center for Psychiatric Neuroscience, Lausanne University Hospital (CHUV), Switzerland.

d. Psychiatric Liaison Service, Lausanne University Hospital (CHUV), Switzerland.

e. Mobile Psychiatry Unit, Department of Psychiatry, Prangins Psychiatric Hospital (CHUV), Switzerland.

E-mail addresses: philippe.golay@chuv.ch, luis.alameda-fernandez@chuv.ch, nadir.mebdouhi@chuv.ch, philipp.baumann@chuv.ch, carina.ferrari@chuv.ch, alessandra.solida@chuv.ch, pierre.progin@chuv.ch, julien.elowe@chuv.ch, philippe.conus@chuv.ch

Corresponding Author: Philippe Golay, Department of psychiatry, Lausanne University Hospital, Consultations de Chauderon, Place Chauderon 18, 1003 Lausanne, Switzerland. Tel: +41213147746; Fax: +41213141277; Email address: Philippe.Golay@chuv.ch

Conflit of interest with respect to the study and manuscript

The authors have declared that there are no conflicts of interest in relation to the subject of the study.

Role of the Funding Source

This study was supported by the Swiss National Science Foundation (#320030_122419 to P.C.); This study was based on institutional funding.

Acknowledgment

We wish to thank the case managers from the TIPP Program for their invaluable work for collecting this data over the years. We also express our gratitude to all patients for their enduring participation. PB was financially supported by Leenaards Foundation.

ABSTRACT

Background: While there is suggestion that early onset of psychosis is a determinant of outcome, knowledge regarding correlates of later onset age is more limited. This study explores the characteristics of patients developing psychosis after age 26, towards the end of the usual age range of early intervention programs, in order to identify potential specific needs of such patients.

Methods: 256 early psychosis patients aged 18-35 were followed-up prospectively over 36 months. Patients with onset after 26 (“later onset”, LO) were compared to the rest of the sample.

Results: LO patients (32% of the sample) had shorter DUP, were less likely to be male, had better premorbid functioning and were more likely to have been exposed to trauma. They had greater insight at presentation and less negative symptoms overall. The trajectories for positive and depressive symptoms were similar in both groups. Evolution of functional level was similar in both groups, but while LO patients recovered faster, they were significantly less likely to return to premorbid functional level.

Conclusions: Later psychosis onset correlates with better pre-morbid functioning and higher rate of trauma exposure; the latter should therefore be a treatment focus in such patients. LO patients were less likely to return to premorbid functional level, which suggests that current treatment strategies may not be efficient to help patients maintain employment. The possibility of distinct illness mechanisms according to onset age and the more central role for trauma in patients with onset after age 26 needs to be further explored.

Key words: age of onset, early psychosis, early intervention, trauma

1. INTRODUCTION

Textbooks usually list early age of onset (before age 18) as a rather robust predictor of poor outcome in schizophrenia. It is well documented that early onset schizophrenia is characterized by a progressive beginning rather than acute onset, associated with enduring negative symptoms followed by attenuated positive symptoms [1-3]. Some results in the literature are nevertheless inconsistent, available papers showing either a positive [4], a negative [5] or the absence of any effect [6, 7]. Age of onset is also correlated with different courses of cognitive deterioration [8, 9]. Most importantly, it has been shown that age at onset is a stronger determinant of neurocognition and social cognition levels than the age at the time of assessment [9, 10].

Much fewer papers have explored the implications of late (onset after age 45) and very late (after 65) onset of schizophrenia, but available data suggest it may correlate with more positive symptoms and less negative symptoms [11, 12]. Although inconsistent, these elements strongly suggest that age at onset may determine specific needs and outcomes in psychosis patients.

Early intervention programs, most commonly providing treatment to patients aged 18 to 35, aim at proposing interventions geared to specific patients' needs. Based on our clinical observation, we realized that patients with a "later onset" (after age 26) often deal with specific challenges and displayed a different pattern of outcome than patients with earlier onset. Liu et al. [13] have found, through admixture analysis, that age 19 and 26 were relevant cut-off to identify clusters in early psychosis (EP) samples, and while most early psychosis programs in Australia do not include patients after age 26 [14], previous publications have shown that the proportion of patients with an onset after 26 is substantial [14, 15]. On this basis we explore in this paper premorbid, baseline and outcome characteristics of patients with psychosis onset after age 26 ("later onset ", LO) and compare them to the other patients of our EP sample.

2. MATERIAL AND METHODS

2.1 Procedure and participants

Launched in 2004 at the Department of Psychiatry in Lausanne University Hospital, Switzerland, the Treatment and early Intervention in Psychosis Program (TIPP) is a specialized early psychosis program. Inclusion criteria are age between 18-35; living in catchment area (population about 300'000) and meeting criteria for psychosis, as defined by the 'psychosis threshold' subscale of the Comprehensive Assessment of At Risk Mental States (CAARMS) scale [16]. The program is a public integrated program which offers outpatient case management, assertive community treatment and an inpatient unit for a 36 months period. Patients can be addressed to TIPP from any psychiatric facility as soon as a diagnosis of psychosis is made and as long as patients have not had more than 6 months of previous treatment for psychosis. The program has been detailed elsewhere [17]. If patients have psychosis related to intoxication or organic brain disease, an intelligence quotient < 70 or have been taking antipsychotic medication for more than six months, patients are referred to other programs. This allows admission of patients who would have been treated unsuccessfully for a small amount of time, and we therefore refer to early psychosis (EP) rather than to first episode psychosis (FEP). Access to the TIPP clinical data was granted by the Ethics Committee of the Faculty of Biology and Medicine of Lausanne University, and consequently all patients who received treatment within this program were included in this study.

2.2 Measures

An *ad hoc* questionnaire was completed by the case managers (CM) who have up to a hundred contacts with patients during the 36 months of treatment. The case manager (CM) is a clinician

(either a psychiatric nurse or a social assistant) who both coordinates and provides treatment and follow up to patient, along with a psychiatrist, over the entire 36 months treatment period; CMs are available for up to 2 home visits per week and on average patients have more than 100 contacts with CM over the treatment period.[17, 18].The questionnaire allows the detailed evaluation of past medical history, demographic characteristics, exposure to adverse life events as well as symptoms and functioning. It is completed on the basis of information gathered from both patients and family during the beginning of treatment. Should new information emerge, it can be updated at any time during follow up. At baseline and after 2, 6, 12, 18, 24, 30 and 36 months of treatment, a series of assessments focused on the evolution of symptoms and functional level are conducted by a psychologist and by case managers. This study is based on the prospective follow-up of the first 256 patients who were treated at TIPP.

2.2.1 Diagnostic Assessment

Expert consensus based diagnosis results from the following elements: Diagnosis reported by a treating psychiatrist (all medical documents including discharge documents after hospital admissions) and assessment by case managers over the 36 months of treatment. The consensus is carried out by a senior psychologist (CF) who is in charge of scale based assessment over the follow-up and a senior psychiatrist (LA). The entire file is reviewed after 18 and 36 months, or at discharge. The diagnostic process is based on criteria from the DSM-IV [19]. In this paper, only the final diagnosis was used.

2.2.2 Sociodemographic, clinical and functional data at baseline

Duration of untreated psychosis (DUP) is defined as the time between onset of psychotic symptoms defined by CAARMS and admission to TIPP. Socio-economic status (SES) was

subdivided into low, intermediate and high [20]. Functional characteristics at baseline were assessed according to both the Modified Vocational Status Index and the Modified Location Code Index Independent living [MVSI & MLCI; 21]. Migration in adversity was considered when migration occurred in adverse contexts such as: seeking protection for political reasons, threat of death, exposure to war or extreme poverty.

Past psychiatric diagnoses were assessed according to DSM-IV criteria [19] while past suicide attempts were listed using ICD-10 classification [22]. Premorbid functional level was evaluated with the Premorbid Adjustment Scale [PAS; 23]. Academic and social sub-scores were computed as well as childhood and early adolescence sub-scores [24]. Past history of trauma was evaluated by case managers over the entire treatment phase and in the context of a trusting relationship [25, 26]. In this study patients were considered exposed to trauma if they had faced at least one experience of sexual or physical abuse prior the age of 16. Past diagnosis of substance abuse or dependence was rated according to DSM-IV criteria by case managers.

The Global Assessment of Functioning [GAF; 19] and the Social and Occupational Functioning Assessment Scale [SOFAS; 19] were used in order to assess the functional level at baseline. While GAF also includes the intensity of symptoms, SOFAS only takes social and occupational level into account. The lowest SOFAS and GAF score before presentation was also estimated. Insight into illness was evaluated as complete, partial or absent on the basis of one item [27].

2.2.3 Outcome measures after 2, 6, 12, 24, and 36 months of follow-up:

Psychopathology and functional level were scored at each assessment, with SOFAS, GAF, the Positive and Negative Syndrome Scale [PANSS; 28] and the Montgomery-Asberg Depression Rating Scale [MADRS; 29]. A psychologist who was independent of patients' treatment and had received standardized training prior to the study conducted the symptoms assessment. For the

PANSS, Inter rater agreement standards [30] were confirmed through training with video-taped interviews and consensus reference ratings.

2.2.4 Outcomes definitions at discharge

Symptomatic remission at discharge was defined at the last PANSS assessment of the last year of the program following Andreasen's Criteria [mild or lower (≤3) score on the following items: delusion, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms, blunted affect, social withdrawal & lack of spontaneity; 31]). Functional recovery was defined as a final PAS score equal or lower to the premorbid rating on four of the five PAS general scale's items [32]. Items on education and abruptness in the change in work were ignored, considering they could not have changed during the period of interest [27]. Patients were considered as "living independently" on the basis of the MLCI (head of household / living alone, with partner, or with peers / living with family with minimal supervision). Patients were considered as "working" at discharge on the basis of the MVSI (paid or unpaid full- or part-time employment / being an active student in school or university / head of household with employed partner (homemaker) /full or part-time volunteer).

2.3 Statistical analysis

All comparisons were performed in the same metric with a series of logistic regression with age of onset (early/late) as the dependent variable, and the individual premorbid and service entry variables as predictors. Because gender and DUP differed in the baseline comparison, all further models were adjusted for these variables. In order to evaluate the impact of age of onset as a continuous variable, linear regressions, logistic regressions or general linear models were estimated with regards to the nature of each outcome (continuous & ordinal, dichotomous

respectively nominal). These models were also adjusted for gender and DUP. Standardized β, odd ratios (Exp(β)) and partial eta squares (ηp^2) were reported together with indication of statistical significance. Mixed effects models repeated measures analysis of variance (MMRM) was used to determine group differences over time on the different measures. Time was introduced as a within-group factor and age of onset as a between-groups factor. From the model, the main effects for age of onset and time can be examined as well as their interaction. Being interested in contrasting change from first assessment to different endpoints and considering the numerous available measurements, planned comparisons within the MMRM were performed. It allowed us to test between group differences regarding rate of improvement in symptoms/functioning from first assessment to various endpoints. Gender and DUP were covariates. The selection of the optimal within-subject covariance matrix was determined with the AIC coefficient. Unstructured, autoregressive, compound-symmetric and Toeplitz structures were tested, including heterogeneous versions of these structures. Variants including age of onset as a continuous variable were also estimated. All statistical analyses were performed with IBM-SPSS 23. All statistical tests were two-tailed and significance was determined at the .05 level.

3. RESULTS

3.1 Sociodemographic and clinical data according to age of onset

LO patients had shorter duration of untreated psychosis (p=.004) and were less likely to be male (p=.002). They had higher level of education (p=.036) while having similar socio-economic level. They were more likely to be married (p<.001) or divorced (p=.046). LO patients were less likely to be students (p=.002) but unemployment rates were very similar in both groups. LO patients were more likely to live independently (p<.001) and they had a better premorbid functioning overall (p =.029) in all specific domains (childhood p=.030; early adolescence

p=.012, social p=.010), except in academic achievement, were there was no group difference (p =.150). When treated as a continuous variable, later onset was also associated with better academic achievement (p =.002). While rates of past suicide attempt were similar between groups, later age of onset was associated with less past suicide attempt (p=.030) when this variable was treated as continuous. LO patients had higher rates of exposure to severe trauma (p=.034), and were more likely to be migrant in adversity (p =.004); they were however less likely to have lifetime alcohol abuse according to the DSM criteria (p =.002) and had greater insight at admission (p=.043). When treated as a continuous variable, age of onset had no significant effect on lifetime alcohol abuse. Functional level at baseline and diagnostic repartition were similar in both groups.

Table 1 about here

3.2 Clinical and functional outcome during the three years of follow up

Disengagement rate was similar in both groups. Symptomatic and functional outcomes were similar as well, except that LO patients were less likely to return to premorbid level of functioning (p=.002).

Table 2 about here

Results of the longitudinal analyses revealed that both main effect of time ($F_{6,194.721}$=5.516, p<.001) and age of onset ($F_{1,194.280}$=4.071, p =.045) on the PANSS negative scores were significant. This indicated that patients' negative symptomatology decreased during the program and that LO patients showed less severe negative symptoms overall (Figure 1a). However planned comparison did not reveal differences in rate of improvement between baseline and different endpoints. When age of onset was considered as a continuous variable, it was

however not significantly related to negative symptomatology. The main effect of time on the PANSS positive scores was significant ($F_{6, 219.865}$=4.006, p=.001) indicating that positive symptomatology of patients globally decreased over time regardless of onset age. The main effect of age of onset did not reveal significant differences between groups when all measurement occasions were taken into account. The trajectory of both groups across time was not affected by age of onset (see Figure 1b). The results were the same when age was taken as a continuous variable. Similarly, when MADRS scores were considered, trajectories of symptoms were similar in both groups and we only observed the main effect of time on symptoms levels ($F_{6,225.656}$=10.338, p<.001). When age was considered as a continuous variable, results were similar.

Figures 1a and 1b about here

Regarding SOFAS scores, a main effect of time could be observed ($F_{7,496.963}$=63.607, p<.001) indicating that patients increased their functioning during the program. While the main effect of age of onset proved to be not significant even when treated as a continuous variable, planned comparison contrasting change from baseline to 2 months indicated that LO patients experienced a faster recovery (t(1219.621)=2.728, p =.006). From month 6 to 36, both groups displayed similar functional levels. Regarding GAF scores, when functioning was based on GAF, there was a main effect for time ($F_{7,551.916}$=56.945, p<.001) but no effect of age of onset even when treated as a continuous variable could be highlighted. The difference in rate of change over the first 2 months was not significant.

Figures 2a and 2b about here

4. DISCUSSION

The purpose of this study was to explore the premorbid, baseline and outcome profile of EP patients with an onset after age 26, in order to see if there were suggestions for particular

treatment needs in this patient group. In line with our hypothesis, LO patients displayed characteristics that may justify a specific therapeutic approach.

One third of the sample had an onset after age 26, which is comparable to previous reports in similar programs [14, 15]. In line with other studies [33, 34], LO patients displayed a shorter DUP, which may be explained by a better social integration at the time of onset and hence a swifter reaction from close relatives or professional colleagues when symptoms became manifest. It could also be linked to a better knowledge of the health care system and a lower reluctance to get treatment than in younger patients. In addition, it is possible that once out of the adolescence phase, where psychotic symptoms are sometimes mistaken for more minor behavioural problems, psychotic symptoms emerging at a later age are less likely to be minimized. Finally, it is also possible that onset of psychosis is more progressive when it occurs earlier while it is more abrupt when occurring later in life.

LO patients were significantly more likely to have been exposed to severe trauma or to have a history of migration in adversity. Greenfield et al. [15] highlighted that the majority of patients over 35 years had experienced trauma, but suggested this may have been linked to the higher proportion of female patients in their later onset subgroup, an observation confirmed in other studies [14, 35-38]. However, when adjusting all analysis for gender, the differences we observed remained significant, suggesting exposure to trauma is indeed an important characteristic of such patients. In line with others [39-42] we observed in a previous study that exposure to adverse experiences during childhood is associated with poorer functional [25] and symptomatic [26] recovery; the fact that LO patients were more likely to have been exposed to trauma may hence play a role in their failure to return to their pre-morbid functional level. Considering this, particular attention should be paid to the exploration of trauma history in LO patients in order to provide adequate support and psychological intervention.

In addition, we observed that, despite better premorbid functional levels, LO patients had similar functional levels at baseline and at the end of the treatment phase when compared to patients with earlier onset. Although they improved faster on the basis of SOFAS scores, LO patients were also significantly less likely to return to premorbid functional levels. While this may seem somehow tautological considering LO patients had more to lose regarding functional levels than patients with an earlier onset as suggested by Riecher-Rössler et al. [43], this observation is nevertheless concerning. Indeed, it suggests that our specialized program fails to help patients maintain the competences they developed over the years before illness onset. Considering this, new strategies need to be implemented regarding vocational intervention as well as the socio-political level, in order to better protect the professional status of patients when they develop psychosis [44].

In line with previous publications [11] there were no differences between both patients groups regarding symptomatic profile, except that LO patients displayed significantly less negative symptoms over the course of the program. This finding has to be tempered by the fact that the impact of age of onset as a continuous variable failled to reach statistical significance suggesting this finding is not very robust. Similarly we did not observe significant differences regarding diagnostic repartition according to age of onset.

Taken together, all these elements suggest that age at the time of emergence of psychosis may be based on distinct illness mechanisms. Patients with earlier onset seem to display a more progressive illness process, starting in childhood as suggested by early disruption of premorbid adjustment, lower academic achievements and global lower premorbid level of functioning. This trajectory is more often complicated by substance abuse and outcome is relatively poor. On the other hand, LO patients seem to have displayed a good premorbid adjustment through the early

phases of life, which allowed them to study, develop a career and social relationships. Considering the high rate of exposure to trauma in these patients, it could be suggested that the underlying illness mechanism is more likely to be driven by environmental factors with a more abrupt onset. This hypothesis is also supported by the observation that patients with a family history of schizophrenia have an earlier onset of illness [45-47]. However, while our data suggest that the age of onset may reflect differences in the underlying pathophysiology, more research is warranted to confirm this hypothesis. Indeed, different causal or risk factors could contribute with a differential weight, but also share many underlying mechanisms.

This study has some limitations. First, while the sample is relatively large, the prevalence of the various characteristics we explored, such as trauma exposure, is small and our results should therefore be replicated in larger samples. Secondly, the age range of patients included in our sample is truncated and excludes patients younger than 18. This prevents the inclusion of patients with very young age at onset of the illness, which may greatly influence the results. However, considering the high number of early intervention programs applying this age range as inclusion criteria, our opinion is that the results of this study are useful considering they identify specific characteristics of LO patients and suggest they may deserve a specific approach.

4.1 Conclusion

Age at the onset of psychosis is the marker of distinct patient profiles. Patients with onset after 26 years may need specific psychological intervention considering their higher likelihood to have been exposed to trauma. In addition, more effort should be made to protect their functional level and prevent their failure to return to the functional level they had attained before illness onset.

The possibility of distinct illness mechanisms according to age of onset of psychosis needs to be explored considering it may pave the way to more specific and personalized interventions.

REFERENCES

1. De Haan L, Bakker J. Overview of neuropathological theories of schizophrenia: from degeneration to progressive developmental disorder. Psychopathology. 2004;37(1):1-7.
2. Eggers C. Some remarks on etiological aspects of early-onset schizophrenia. European child & adolescent psychiatry. 1999;8(1):S1-S4.
3. Poustka L, Parzer P, Brunner R, Resch F. Basic symptoms, temperament and character in adolescent psychiatric disorders. Psychopathology. 2007;40(5):321-8.
4. Bland RC, Parker JH. Prognosis in schizophrenia: prognostic predictors and outcome. Archives of General Psychiatry. 1978;35(1):72-7.
5. Juola P, Miettunen J, Veijola J, Isohanni M, Jääskeläinen E. Predictors of short–and long-term clinical outcome in schizophrenic psychosis–the Northern Finland 1966 Birth Cohort study. European Psychiatry. 2013;28(5):263-8.
6. Üçok A, Gorwood P, Karadayı G. Employment and its relationship with functionality and quality of life in patients with schizophrenia: EGOFORS Study. European Psychiatry. 2012;27(6):422-5.
7. Schimmelmann BG, Conus P, Cotton S, McGorry PD, Lambert M. Pre-treatment, baseline, and outcome differences between early-onset and adult-onset psychosis in an epidemiological cohort of 636 first-episode patients. Schizophrenia research. 2007;95(1):1-8.
8. Zaytseva Y, Korsakova N, Gurovich I. Course of cognitive functioning in first episode of schizophrenia prior to the age of onset: 5-year follow up study. European Psychiatry. 2010;25:1716.
9. Linke M, Jankowski KS, Ciołkiewicz A, Jędrasik-Styła M, Parnowska D, Gruszka A, et al. Age or age at onset? Which of them really matters for neuro and social cognition in schizophrenia? Psychiatry research. 2015;225(1):197-201.
10. Rajji TK, Voineskos AN, Butters MA, Miranda D, Arenovich T, Menon M, et al. Cognitive performance of individuals with schizophrenia across seven decades: a study using the MATRICS consensus cognitive battery. The American Journal of Geriatric Psychiatry. 2013;21(2):108-18.
11. Howard R, Castle D, Wessely S, Murray R. A comparative study of 470 cases of early-onset and late-onset schizophrenia. The British journal of psychiatry. 1993;163(3):352-7.
12. Howard R, Rabins PV, Seeman MV, Jeste DV. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. American Journal of Psychiatry. 2000.
13. Liu JJ, Norman RM, Manchanda R, De Luca V. Admixture analysis of age at onset in schizophrenia: evidence of three subgroups in a first-episode sample. General hospital psychiatry. 2013;35(6):664-7.
14. Selvendra A, Baetens D, Trauer T, Petrakis M, Castle D. First episode psychosis in an adult area mental health service—a closer look at early and late-onset first episode psychosis. Australasian Psychiatry. 2014;22(3):235-41.
15. Greenfield P, Joshi S, Christian S, Lekkos P, Gregorowicz A, Fisher HL, et al. First episode psychosis in the over 35 s: is there a role for early intervention? Early intervention in psychiatry. 2016.
16. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Australian and New Zealand Journal of Psychiatry. 2005;39(11-12):964-71.
17. Baumann PS, Crespi S, Marion-Veyron R, Solida A, Thonney J, Favrod J, et al. Treatment and Early Intervention in Psychosis Program (TIPP-Lausanne): implementation of an early intervention programme for psychosis in Switzerland. Early intervention in psychiatry. 2013;7(3):322-8.

18. Marion-Veyron R, Mebdouhi N, Baumann PS, Thonney J, Crespi S, Conus P. Les premiers épisodes psychotiques: de l'importance du case management. L'Évolution Psychiatrique. 2013;78(1):41-51.
19. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM). Washington, DC: American psychiatric association. 1994:143-7.
20. Chandola T, Jenkinson C. The new UK National Statistics Socio-Economic Classification (NS-SEC); investigating social class differences in self-reported health status. Journal of Public Health. 2000;22(2):182-90.
21. Tohen M, Hennen J, Zarate Jr CM, Baldessarini RJ, Strakowski SM, Stoll AL, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. American Journal of Psychiatry. 2000;157(2):220-8.
22. Dilling H, Dittmann V. [Psychiatric diagnosis following the 10th revision of the International Classification of Diseases (ICD-10)]. Der Nervenarzt. 1990;61(5):259-70.
23. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophrenia Bulletin. 1982;8(3):470.
24. MacBeth A, Gumley A. Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical reappraisal. Acta Psychiatrica Scandinavica. 2008;117(2):85-99.
25. Alameda L, Ferrari C, Baumann P, Gholam-Razaee M, Do KQ, Conus P. Childhood sexual and physical abuse: age at exposure modulates impact on functional outcome in early psychosis patients. Psychological medicine. 2015;45(13):2727-36.
26. Alameda L, Golay P, Baumann P, Ferrari C, Do KQ, Conus P. Age at the time of exposure to trauma modulates the psychopathological profile in early psychosis patients. Journal of Clinical Psychiatry. 2016;77(5):e612-e8.
27. Conus P, Cotton S, Schimmelmann BG, McGorry PD, Lambert M. The First-Episode Psychosis Outcome Study: premorbid and baseline characteristics of an epidemiological cohort of 661 first-episode psychosis patients. Early intervention in Psychiatry. 2007;1(2):191-200.
28. Kay SR, Flszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin. 1987;13(2):261.
29. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. The British journal of psychiatry. 1979;134(4):382-9.
30. Kay SR, Opler LA, Spitzer RL, Williams JB, et al. SCID-PANSS: Two-tier diagnostic system for psychotic disorders. Comprehensive Psychiatry. 1991;32(4):355-61.
31. Andreasen NC, Carpenter Jr WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. American Journal of Psychiatry. 2005;162(3):441-9.
32. Strakowski SM, Keck PE, McElroy SL, West SA, Sax KW, Hawkins JM, et al. Twelve-month outcome after a first hospitalization for affective psychosis. Archives of General Psychiatry. 1998;55(1):49-55.
33. Apeldoorn S, Sterk B, van den Heuvel E, Schoevers R, Islam M, Investigators OoP. Factors contributing to the duration of untreated psychosis. Schizophrenia research. 2014;158(1):76-81.
34. Schimmelmann BG, Huber CG, Lambert M, Cotton S, McGorry PD, Conus P. Impact of duration of untreated psychosis on pre-treatment, baseline, and outcome characteristics in an epidemiological first-episode psychosis cohort. Journal of psychiatric research. 2008;42(12):982-90.
35. Castle DJ. Women and schizophrenia: an epidemiological perspective. Women and schizophrenia Cambridge University Press, Cambridge. 2000:19-34.
36. Harris MJ, Jeste DV. Late-onset schizophrenia: an overview. Schizophrenia Bulletin. 1988;14(1):39.

37. Harvey P. Late-onset schizophrenia: characteristics of patients at the first episode. The early course of schizophrenia. 2006:175.
38. Thorup A, Waltoft BL, Pedersen CB, Mortensen PB, Nordentoft M. Young males have a higher risk of developing schizophrenia: a Danish register study. Psychological medicine. 2007;37(04):479-84.
39. Lysaker PH, Nees MA, Lancaster RS, Davis LW. Vocational function among persons with schizophrenia with and without history of childhood sexual trauma. Journal of traumatic stress. 2004;17(5):435-8.
40. Conus P, Cotton S, Schimmelmann BG, McGorry PD, Lambert M. Pretreatment and outcome correlates of sexual and physical trauma in an epidemiological cohort of first-episode psychosis patients. Schizophrenia bulletin. 2010;36(6):1105-14.
41. Stain HJ, Brønnick K, Hegelstad WT, Joa I, Johannessen JO, Langeveld J, et al. Impact of interpersonal trauma on the social functioning of adults with first-episode psychosis. Schizophrenia bulletin. 2013:sbt166.
42. Trotta A, Murray RM, David AS, Kolliakou A, O'Connor J, Di Forti M, et al. Impact of different childhood adversities on 1-year outcomes of psychotic disorder in the genetics and psychosis study. Schizophrenia bulletin. 2016;42(2):464-75.
43. Riecher-Rössler A, Häfner H. Gender aspects in schizophrenia: bridging the border between social and biological psychiatry. Acta Psychiatrica Scandinavica. 2000;102(s407):58-62.
44. Dutoit M, Besse C, Hausmann P, Spagnoli D, Bonsack C. Une expérience de soutien à l'emploi pour les personnes souffrant de troubles psychiques en Suisse romande. Rev Med Suisse. 2014;10:1711-4.
45. Chase GA, Cohen B. A chart review study of late-onset and early-onset schizophrenia. Am J Psychiatry. 1989;146(12):1569.
46. Howard R, Graham C, Sham P, Dennehey J, Castle D, Levy R, et al. A controlled family study of late-onset non-affective psychosis (late paraphrenia). The British Journal of Psychiatry. 1997;170(6):511-4.
47. Jeste DV, Symonds LL, Harris MJ, Paulsen JS, Palmer BW, Heaton RK. Nondementia nonpraecox dementia praecox?: late-onset schizophrenia. The American Journal of Geriatric Psychiatry. 1997;5(4):302-17.

Table 1. Sociodemographic and clinical data according to age of of onset.

	Total	< 26 year	≥ 26 year	Odd ratio	95% CI of OR		p-value	Influence of age of onset as a continuous variable
	N =256	N = 175 (68.4%)	N = 81 (31.6%)		LCI	UCI		
Age of onset in year, M (SD)	23.14 (5.21)	20.27 (3.30)	29.35 (2.40)	-	-	-	-	-
Age in year, M (SD)	24.56 (4.833)	21.97 (3.041)	30.16 (2.817)	2.680	2.01	3.571	<.001	β=.882**
Duration of untreated psychosis (days), Mdn (IQR)[a]	90.50 (480.25)	127.00 (584.00)	55.0 (141.00)	0.634	0.464	0.866	.004	β=-.281**
Gender, male, % (N)	64.5 (165)	70.9 (124)	50.6 (41)	2.372	1.377	4.087	.002	Exp(β)=1.056*
Socio-economical level, % (N)								
Low	17.6 (45)	17.7 (31)	17.3 (14)	Ref.cat.	-	-	-	β=.008
Intermediate	44.9 (115)	44.0 (77)	46.9 (38)	1.199	0.554	2.592	.645	
High	37.5 (96)	38.3 (67)	35.8 (29)	1.054	0.476	2.338	.896	
Education in year, M (SD)	9.81 (2.84)	9.53 (2.53)	10.48 (3.40)	1.129	1.008	1.263	.036	β=.189**
Marital status, % (N)								
Single	82.8 (207)	91.1 (154)	65.4 (53)	Ref.cat.	-	-	-	ηp^2=.162**
Married	9.2 (23)	3.6 (6)	21.0 (17)	9.244	3.246	26.321	<.001	
Divorced	3.2 (8)	1.8 (3)	6.2 (5)	4.793	1.025	22.421	.046	
Cohabitation	4.8 (12)	3.6 (6)	7.4 (6)	2.476	0.731	8.380	.145	
Professional activity, % (N)								
Full time job	13.2 (33)	11.6 (20)	16.7 (13)	Ref.cat.	-	-	-	ηp^2=.136**
Student/Traineeship	17.2 (43)	22.7 (39)	5.1 (4)	0.136	0.037	0..495	.002	
Part time job	2.4 (6)	2.3 (4)	2.6 (2)	0.648	0.093	4.487	.660	
Disability annuity	3.6 (9)	2.3 (4)	6.4 (5)	2.827	0.550	14.542	.214	
On Sickness leave	18.0 (45)	17.4 (30)	19.2 (15)	0.938	0.348	2.529	.899	
Unemployed	45.6 (114)	43.6 (75)	50.0 (39)	0.999	0.427	2.341	.999	
Lifestyle, % (N)								
Family	41.1 (101)	54.2 (91)	12.8 (10)	Ref.cat	-	-	-	ηp^2=.334**
Independent household	14.9 (25)	53.8 (42)	16.211	6.874	38.231	<.001		
With friends	27.2 (67)	18.5 (31)	29.5 (23)	7.146	2.972	17.181	<.001	
Pension / care home	22.0 (54)	4.8 (8)	2.6 (2)	3.425	0.602	19.487	.165	
Unsettled (hotel, shelter homeless)	4.1 (10) 5.7 (14)	7.7 (13)	1.3 (1)	1.104	0.125	9.775	.929	
Premorbid Adj. (PAS) M (SD)	0.30 (0.19)	0.32 (0.20)	0.25 (0.16)	0.132	0.021	0.818	.030	β=-.201**
Childhood	0.32 (0.17)	0.34 (0.18)	0.27 (0.13)	0.074	0.010	0.564	.012	β=-.321**
Early adolescence	0.29 (0.21)	0.32 (0.22)	0.23 (0.18)	0.104	0.018	0.583	.010	β=-.267**
Social	0.35 (0.20)	0.37 (0.20)	0.31 (0.18)	0.306	0.061	1.535	.150	β=-.222**
Academic	0.31 (0.17)	0.33 (0.18)	0.26 (0.14)	0.089	0.010	0.776	.029	β=-.286**
Total								
Past suicide attempt, % (N)	14.5 (35)	16.5 (27)	10.3 (8)	0.513	0.213	1.235	.136	Exp(β)=0.919*
History of trauma[b], % (N)	27.8 (71)	24.0 (42)	36.3 (29)	1.923	1.051	3.519	.034	Exp(β)=1.067*
Migration in adversity, % (N)	28.2 (72)	22.9 (40)	40.0 (32)	2.455	1.343	4.489	.004	Exp(β)=1.066*
Born in Switzerland, % (N)	54.3 (139)	62.3 (109)	37.0 (30)	0.322	0.181	0.572	<.001	Exp(β)=0.905**
Forensic history, % (N)	13.1 (29)	11.5 (18)	17.2 (11)	2.141	0.899	5.099	.085	Exp(β)=1.027

Offences during program, % (N)	12.0 (13)	15.5 (11)	5.4 (2)	0.387	0.078	1.906	.243	Exp(β)=0.921
Psychiatric history, % (N)	62.3 (157)	65.9 (114)	54.4 (43)	0.627	0.350	1.121	.115	Exp(β)=0.978
Familial psychiatric history, % (N)	62.8 (147)	63.0 (104)	62.3 (43)	1.066	0.583	1.950	.836	Exp(β)=1.001
Familial schizophrenia history, % (N)	24.1 (47)	27.3 (36)	17.5 (11)	0.642	0.296	1.395	.263	Exp(β)=0.975
Lifetime substance abuse (DSM), % (N)								
Alcohol	26.0 (63)	33.5 (56)	9.3 (7)	0.251	0.106	0.595	.002	Exp(β)=0.941
Cannabis	39.7 (96)	45.0 (76)	27.4 (20)	0.556	0.296	1.045	.068	Exp(β)=0.946
Other substances	14.4 (36)	15.2 (26)	12.7 (10)	0.941	0.417	2.122	.883	Exp(β)=1.012
Lifetime substance addiction (DSM), % (N)								
Alcohol	9.9 (24)	11.3 (19)	6.7 (5)	0.740	0.254	2.155	.581	Exp(β)=1.023
Cannabis	31.8 (77)	36.7 (62)	20.5 (15)	0.554	0.281	1.093	.089	Exp(β)=0.958
Other substances	7.2 (18)	8.2 (14)	5.1 (4)	0.620	0.190	2.019	.427	Exp(β)=1.002
Insight at presentation, % (N)								
Absent	36.7 (90)	38.3 (64)	33.3 (26)	Ref. cat.	-	-	-	β=.096
Partial	45.7 (112)	47.9 (80)	41.0 (32)	1.020	0.539	1.930	.952	
Complete	17.6 (43)	13.8 (23)	25.6 (20)	2.241	1.024	4.903	.043	
GAF, M (SD)								
Baseline	36.93 (16.29)	36.40 (16.03)	38.05 (16.91)	1.003	0.986	1.021	.700	β=.051
Worst during psychosis	25.40 (10.96)	25.39 (10.74)	25.41 (11.47)	0.999	0.973	1.025	.913	β=.009
SOFAS, M (SD)								
Baseline	39.03 (15.61)	38.92 (15.119)	39.25 (16.69)	1.001	0.984	1.019	.911	β=.037
Worst during psychosis	28.43 (11.97)	28.69 (11.78)	27.92 (12.40)	0.997	0.973	1.021	.798	β=.017
CGI, M (SD)								
Baseline	4.91 (1.36)	4.98 (1.31)	4.77 (1.46)	0.875	0.706	1.084	.222	β=-.104
Higher during psychosis	5.87 (0.76)	5.89 (0.77)	5.83 (0.74)	0.825	0.556	1.224	.340	β=-.077
Diagnostic, % (N)								ηp^2=.005
Schizophrenia	59.4 (152)	63.4 (111)	50.6 (41)	Ref. cat.	-	-	-	
Schizophreniform/brief	10.2 (26)	9.7 (17)	11.1 (9)	0.938	0.368	2.391	.893	
Schizo-affective	9.8 (25)	7.4 (13)	14.8 (12)	1.790	0.725	4.424	.207	
Major depression[c]	2.3 (6)	1.7 (3)	3.7 (3)	1.982	0.368	10.682	.426	
Bipolar disorder	8.2 (21)	7.4 (13)	9.9 (8)	1.233	0.458	3.320	.679	
Other	10.2 (26)	10.3 (18)	9.9 (8)	0.924	0.358	2.380	.869	

Note. Mdn = Median. IQR = Interquartile range. Ref.cat = reference category. a = Raw data are presented, however the test statistics were based on log10 (+constant) transformed data because of extreme positive skewness; [b] physical or sexual abuse [c] with psychotic features. All model were adjusted for gender and duration of untreated psychosis. * p<.05, ** p<.01.

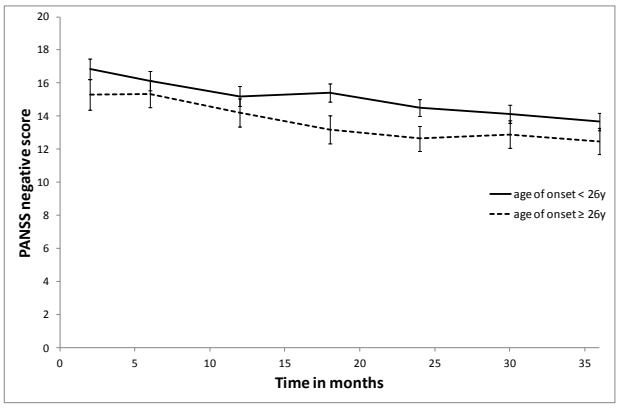
Table 2. Outcomes according to age of of onset.

	Total	< 26 year	≥ 26 year	Odd ratio	95% CI of OR		p-value	Influence of age of onset as a continuous variable
	N =256	N = 175 (68.4%)	N = 81 (31.6%)		LCI	UCI		
Program commitment, % (N)								
Seen at least once	97.8	97.7 (127)	98.2 (54)	2.033	0.193	21.385	.555	Exp(β)=0.938
Interruption > 2 months	(181)	23.4 (30)	23.5 (12)	1.048	0.479	2.293	.907	Exp(β)=1.033
Lost from sight	23.5 (12)	12.6 (16)	13.7 (7)	1.138	0.429	3.019	.796	Exp(β)=1.031
	12.9 (23)							
Follow-up after program, % (N)								
Specialized ambulatory care	51.1 (90)	54.0 (68)	44.0 (22)	Ref. cat.	-	-	-	ηp^2=.029
Other ambulatory care	12.5 (22)	11.9 (15)	14.0 (7)	1.423	0.502	4.035	.507	
Private practice psychiatrist/psychologist	21.6 (38)	19.8 (25)	26.0 (13)	1.220	0.511	2.912	.654	
General practitioner	5.7 (10)	7.1 (9)	2.0 (1)	0.252	0.029	2.164	.209	
No follow-up needed	3.4 (6)	2.4 (3)	6.0 (3)	2.459	0.423	14.313	.317	
Other	5.7 (10)	4.8 (6)	8.0 (4)	1.833	0.452	7.423	.396	
Symptomatic response at the last assessment of the last year of the program (Andreassen), % (N)	50.7 (75)	47.1 (49)	59.1 (26)	1.208	0.545	2.674	.642	Exp(β)=0.999
Functional recovery (PAS) at the last assessment of the last year of the program, % (N)	44.8 (73)	51.8 (59)	28.6 (14)	0.289	0.133	0.630	.002	Exp(β)=0.905**
Functional recovery – independent work, % (N)	24.2 (47)	22.6 (31)	28.1 (16)	1.103	0.532	2.288	.792	Exp(β)=1.014
Functional recovery – independent living, % (N)	56.7 (110)	52.6 (72)	66.7 (38)	1.584	0.817	3.070	.174	Exp(β)=1.069*
Combined functional recovery (indep. work & living), % (N)	20.6 (40)	19.0 (26)	24.6 (14)	1.135	0.526	2.449	.746	Exp(β)=1.023

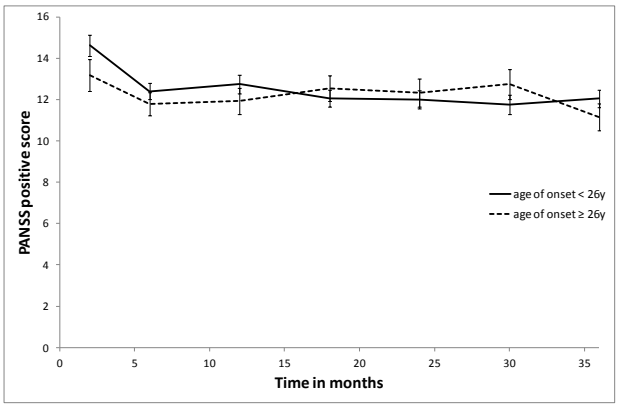
Note. Ref.cat = reference category. All model were adjusted for gender and duration of untreated psychosis. * p<.05, ** p<.01.

Figure 1. PANSS scores over 36 months: Comparisons between early and late onset patients.

1a) PANSS negative score



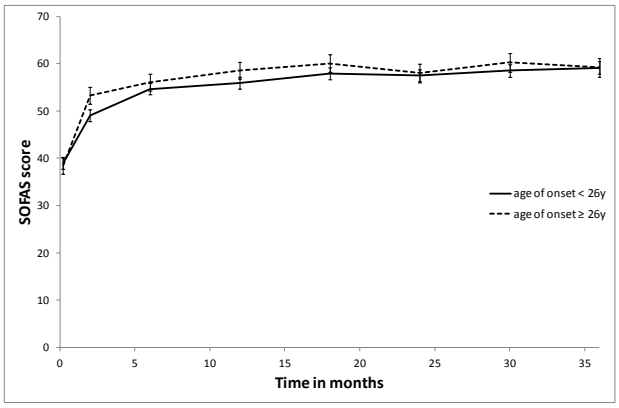
1b) PANSS positive score



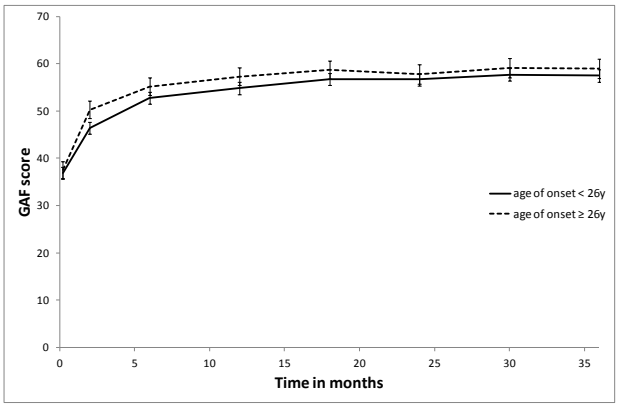
Abbreviations: PANSS = Positive and Negative Syndrome Scale

Figure 2. Functioning scores over 36 months: Comparisons between early and late onset patients.

2a) SOFAS scores



2b) GAF scores



Abbreviations: SOFAS = Social and Occupational Functioning Assessment Scale , GAF = Global Assessment of Functioning