Premorbid Characteristics as Predictors of Early Onset Versus Adult Onset in Patients With a First Episode of Psychosis

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ABSTRACT

Objective: To study the differences in early-life characteristics between patients with an early onset of psychotic disorders (EOP, aged < 18 years) versus adult onset of psychotic disorders (AOP, aged ≥ 18 years) and to identify predictors of earlier onset.

Methods: 278 patients with a first episode of psychosis between the ages of 7 and 35 years were recruited as part of a multicenter prospective longitudinal study conducted in Spain between January 1, 2009, and December 31, 2011, with diagnoses made for AOP using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I) and for EOP using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS). Early-stage factors such as prenatal, perinatal, and other premorbid factors were registered and compared between EOP and AOP patients. To analyze the association between baseline variables and outcome, univariate and multivariate logistic regression models were used, and the association or odds ratios (ORs) for significant risk factors were calculated.

Results: 224 patients with AOP (mean ± SD age = 25.6 ± 5.0 years; 65.6% male) and 54 patients with EOP (16.1 ± 1.7 years; 68.5% male) were included. Univariate analysis revealed significant differences between the groups. Specifically, compared to AOP subjects, EOP patients had more frequent obstetric complications (OCs) ($P < .001$), birth weight < 2.500 g ($P < .028$), a background of any personal psychiatric disorder ($P < .001$), a previous diagnosis of attention-deficit/hyperactivity disorder ($P = .001$), and premorbid IQ < 85 ($P < .001$). In the multivariate model, only OCs (OR = 5.44), personal psychiatric background (OR = 4.05), and IQ < 85 (OR = 3.96) predicted an onset of the first episode of psychosis before age 18 years.

Conclusions: Premorbid factors such as OCs, personal psychiatric background, and IQ < 85 could help predict which patients are more likely to have an early onset of psychosis. Awareness of these factors could help clinicians work to prevent the early transition to psychosis in children and adolescents.

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Schizophrenia is a disease with high personal and societal costs.[1] Age at onset of the illness is a key factor that can have a significant impact on social/occupational functioning and overall outcome (for a review, see Jin and Mosweu[2]). The earlier the age at onset, and the longer the course of the illness, the worse the outcome.[3] Patients with early-onset schizophrenia or psychosis (EOP; ie, those who meet criteria for any psychotic disorder with an onset prior to 18 years of age)[4] are associated with worse medium and long-term outcome.[5] EOP is linked to severe cognitive decline,[6] higher social and intellectual impairment,[7,8] and more negative symptoms, hospitalizations, and relapses.[1]

The neurodevelopmental hypothesis of psychosis[9,10] posits that apart from genetic load, certain early developmental issues could result in an increased risk of psychosis.[11] In a recent systematic review and meta-analysis,[12] a significant number of pre- and perinatal risk factors such as congenital malformations, obstetric complications, birth in winter or early spring, maternal psychosis, and maternal affective disorder were all associated with the onset of a psychotic disorder. Premorbid intelligence quotient has also been linked to age at onset of psychosis. A meta-analysis of population-based studies[13] found an association between greater IQ deficits and earlier age at onset. Additionally,

Clinical Points

- Most research on the first episode of psychosis has focused on adults. However, by studying children, adolescents, and adults together, it has been found that certain premorbid factors may help predict which patients are more likely to have an earlier onset of psychosis.
- Seeking information about obstetric complications and other premorbid characteristics may help clinicians better assess young patients' risk of psychosis.

worse premorbid functioning has been consistently found in patients with earlier-onset versus later-onset psychosis.[14]

It has been suggested that severe disorders such as psychosis are typically preceded by less severe disorders during childhood and adolescence.[15] For example, an alteration of attention early in life has been consistently linked to the later diagnosis of psychosis or schizophrenia,[16] and attention-deficit/hyperactivity disorder (ADHD) is a frequent prior diagnosis or comorbidity in psychotic patients.[17]

Thus, the main aim of this study was to look at a sample of patients with first-episode psychosis (FEP) and compare individuals with early onset (< 18 years) to those with adult onset (≥ 18 years) focusing on prenatal and perinatal complications as well as other premorbid characteristics such as previous diagnoses of personal psychiatric disorders and premorbid IQ. The second goal was to identify predictive factors of the earlier onset of FEP. We hypothesized that in our sample, patients with EOP would have both a higher frequency of pre- and perinatal events and worse premorbid characteristics than adult-onset psychosis (AOP) patients. We also expected to find that some characteristics, such as obstetric complications, could help predict early onset of FEP.

METHODS

Sixteen centers in Spain participated in the PEPs Project, a 2-year prospective longitudinal multicenter study conducted between January 1, 2009, and December 31, 2011, in which 335 patients with FEP and 253 matched healthy controls were included (for a full description of the study design, see Bernardo et al[18]). The main objective of the PEPs Project was to identify different gene-by-environment interactions involved in the risk of psychosis in a naturalistic cohort of FEP patients to help develop a predictive model of psychosis.[19] Most of the centers were part of the Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), which is a well-recognized Spanish Mental Health research network.

Participants

For the present study, the sample from the PEPs Project was examined, and all FEP patients who had obstetric complication (OC) data were included (N = 278). Each patient who met the inclusion criteria and was attended at any of the participating sites was invited to collaborate in the study. The inclusion criteria were (1) age between 7 and 35 years, (2) presence of psychotic symptoms that had begun within the previous 12 months, (3) the ability to speak Spanish, and (4) providing written informed consent. The exclusion criteria were (1) intellectual disability according to *DSM-IV* criteria,[20] including both an IQ < 70 and impaired functioning; (2) history of head trauma with loss of consciousness; and (3) presence of an organic disease with mental repercussions.

The study followed the ethical principles of the Declaration of Helsinki and was approved by the ethics review committee of each center. Informed consent was obtained from all participants or from the parents or legal guardians of underage subjects.

Assessment

The assessments were performed by experienced psychiatrists or psychologists, and the following data were obtained:

- Sociodemographic data, including socioeconomic status (SES), measured with the Hollingshead and Redlich scale,[21] which has 5 possible scores, from I (1) to V (5), with lower numbers indicating better SES.
- Family psychiatric background, determined through an interview with the parents or legal guardians that included questions about first- and second-degree relatives.
- The Obstetric Complication Scale,[22] a 15-item scale measuring 4 prenatal and 11 peri-/postnatal complications. This scale establishes thresholds for rating the items as either "definite" or "equivocal." For our study, each of these ratings was considered an indication of the presence of OC. This follows the broad definition of OCs used by Verdoux et al.[23] Birth weight and parental age at delivery were also registered. The evaluator retrospectively rated information regarding obstetric complications, both from mothers' reports and from local medical records when available.
- Premorbid IQ, assessed with the vocabulary subtest from the Wechsler Intelligence Scale for Children IV (WISC-IV)][24] or the Wechsler Adult Intelligence Scale III (WAIS-III)[25] depending on the age of the patient.
- The Premorbid Adjustment Scale (PAS),[26] which assesses the level of functioning in different domains: sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and social-sexual aspects of life. It explores these domains at 4 different stages of life: childhood (up to age 11 years), early adolescence (12–15 years), late adolescence (16–18 years), and adulthood. The PAS also includes a general subscale with items regarding quality of life, which is to be completed without reference to any specific age or life stage.

Each domain is scored on a scale from 0 (good) to 6 (poor), and there is a total score. The functioning assessed by the PAS covers up to 1 year before the onset of psychotic illness. The subscale regarding adulthood was not used in our comparison analysis since the minors in our sample (EOP patients) were not able to complete it.

- Age at onset of the FEP, calculated using the Symptom Onset in Schizophrenia (SOS) inventory,[27,28] which includes information given by patients, family, and clinicians.
- Past and current diagnoses, made using the Spanish version of the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I)[29] for AOP patients or the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS)[30,31] for EOP patients.

Procedures

For the present analysis, only baseline data were used. The data were obtained from the patients, their parents/legal tutors, and medical records. We divided the sample into two groups, separating subjects whose illness had begun with EOP from those with AOP. The SOS inventory was used to make this determination.

Data Analysis

Quantitative variables were expressed as mean ± SD and qualitative variables as total numbers and percentages. To compare the means of two variables, the Student *t* test was used (or Wilcoxon when applicable). Proportions were compared using the χ^2 or Fisher exact test, as appropriate. Logistic regression analysis was used to study the effects of baseline characteristics in predicting the outcome. A *P* value < .10 was used to screen covariates for inclusion in the multivariate analysis. A backward-stepwise selection algorithm was applied to select covariates for inclusion in the multivariate regression model. At each step, the least significant variable was discarded. To report the effect size, the odds ratio (OR) and 95% CI were calculated. All *P* values are 2-sided and considered statistically significant if < .05. Data were analyzed with R software version 4.0.2 (R project for statistical computing; Vienna, Austria) and IBM SPSS version 23.

Table 1. Sociodemographic, Prenatal, Perinatal, and Premorbid Characteristics of the Sample According to the Age at Onset of Psychosis[a]

Characteristic	EOP Patients (n = 54)	AOP Patients (n = 224)	t/χ^2/OR	*P*
Age, mean ± SD, y	16.1 ± 1.7	25.6 ± 5.0	−13.672	**< .001**
Male	37 (68.5)	147 (65.6)	0.163	.750
SES,[b] mean ± SD	2.9 ± 1.5	3.1 ± 1.3	0.984	.326
Urbanicity (city > 100,000 inhabitants)	35 (64.8)	164 (73.2)	1.509	.241
Migrant	6 (11.1)	30 (13.4)	0.201	.822
Winter/spring birth	29 (53.7)	111 (49.6)	0.300	.650
OCs	33 (61.1)	69 (30.8)	18.235	**< .001**
Birth weight, mean ± SD, g	3,191.8 ± 536.4	3,306.3 ± 530.6	−1.331	.185
Birth weight < 2,500 g[c]	5 (10.4)	5 (2.7)	5.620	**.032**
Familial psychotic background (first or second degree)	10 (18.5)	35 (15.6)	0.269	.680
Maternal psychosis	7 (13)	33 (14.7)	0.111	.832
Maternal affective disorder	5 (9.3)	22 (9.8)	0.016	1.000
Maternal age at delivery, mean ± SD, y	30.5 ± 5.2	28.7 ± 5.6	1.937	.054
Paternal age at delivery, mean ± SD, y	33.3 ± 6.1	31.9 ± 6.9	1.345	.180
Personal psychiatric background[d]	36 (72)	64 (29.9)	30.159	**< .001**
Previous diagnosis of ADHD[d]	8 (14.8)	6 (2.7)	13.401	**.001**
Premorbid IQ, mean ± SD[e]	85.8 ± 14.1	93.4 ± 13.4	−3.307	**.001**
Premorbid IQ < 85	24 (54.5)	58 (32.8)	7.161	**.009**

[a]Values are shown as n (%) unless otherwise noted. Boldface indicates statistical significance.
[b]SES was measured using the Hollingshead and Redlich scale, which has 5 possible scores, from I (1) to V (5), with lower numbers indicating better SES.
[c]Data on birth weight were available for 48 EOP patients and 187 AOP patients.
[d]Data were available for 50 EOP patients and 214 AOP patients.
[e]Data on premorbid IQ were available for 44 EOP patients and 177 AOP patients.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AOP = adult-onset psychosis, EOP = early-onset psychosis, OC = obstetric complication, OR = odds ratio, SES = socioeconomic status.

Table 2. Univariate and Multivariate Models of Predictor Factors of Early-Onset First Episode of Psychosis

	Univariate Model			Multivariate Model		
Predictor	OR	CI	*P*	OR	CI	*P*
OCs	3.53	1.91–6.54	**< .001**	5.44	2.28–13.00	**< .001**
Birth weight < 2,500 g[b]	4.23	1.17–15.27	**.028**			
Personal psychiatric background[c]	6.03	3.04–11.93	**< .001**	4.05	1.71–9.53	**< .001**
Previous diagnosis of ADHD[c]	6.32	2.01–19.08	**.001**			
Premorbid IQ < 85	2.46	1.26–4.82	**.009**	3.96	1.66–9.44	**< .001**
Maternal age at birth	1.06	1.00–1.12	**.05**			

[a]Boldface indicates statistical significance.
[b]Data for 235 patients.
[c]Data for 264 patients.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, OC = obstetric complication, OR = odds ratio.

RESULTS

Sociodemographic and Clinical Characteristics of the Sample

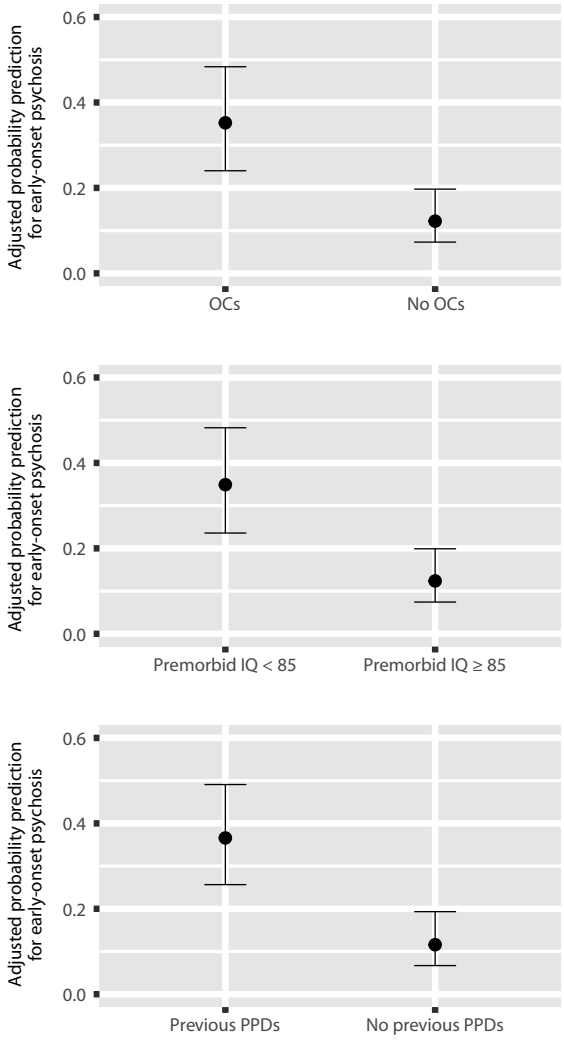
Among the 278 patients included in the study, 224 were AOP patients and 54 EOP patients. Table 1 shows the sociodemographic and prenatal, perinatal, and premorbid characteristics of both subsamples. The number of patients who had OCs, birth weight < 2,500 g, a personal psychiatric background, a previous diagnosis of ADHD, or a premorbid IQ < 85 was statistically higher in the EOP versus the AOP sample (Tables 1 and 2). The most frequent OCs in both groups were the following: cesarean birth or emergency delivery, labor length > 36 hours or < 3 hours, gestational age < 37 weeks or > 42 weeks, and difficult forceps delivery. Among EOP patients with a previous psychiatric diagnosis, the most common diagnoses were ADHD (22.9%), any type of depressive disorder (14.3%), any type of anxiety disorder (14.3%), and eating disorders (11.4%). Among AOP

Table 3. Comparison of Scores on the PAS Between Patients With Early Onset of Psychosis and Those With Adult Onset[a]

PAS Score Category	EOP Patients (n = 54)	AOP Patients (n = 224)	OR	CI	*P*
Childhood (up to age 11 y)	6.8 ± 4.6	6.0 ± 4.0	1.06	0.98–1.13	.129
Early adolescence (12–15 y)[b]	10.8 ± 6.3	8.0 ± 5.0	1.11	1.05–1.17	**<.001**
Late adolescence (16–18 y)[c]	14.1 ± 6.3	9.1 ± 5.6	1.15	1.08–1.23	**<.001**
General	23.6 ± 9.0	19.1 ± 11.4	1.31	1.01–1.07	**.006**
Total	48.2 ± 19.8	45.4 ± 24.1	1.10	0.99–1.02	.288

[a]Values shown as mean ± SD. Boldface indicates statistical significance.
[b]Data on early adolescence were available for 51 EOP participants.
[c]Data on late adolescence were available for 31 EOP participants.
Abbreviations: AOP = adult-onset psychosis, EOP = early-onset psychosis, OR = odds ratio, PAS = Premorbid Adjustment Scale.

Figure 1. Adjusted Probability Prediction for an Early Onset of Psychosis, Comparing Patients With or Without Obstetric Complications (OCs), Previous Personal Psychiatric Disorders (PPDs), and Premorbid IQ < 85



patients, the most common previous diagnoses were any depressive disorder (44%), any anxiety disorder (13.3%), any substance use disorder (12%), and ADHD (6.7%).

PAS subscale scores were significantly different between EOP and AOP patients in early and late adolescence, while the general score was also significantly higher for EOP patients, which is indicative of poorer adjustment. The childhood subscale and total scores did not show statistically significant differences between the samples (Table 3).

Predictor Factors of an EOP

Obstetric complications, personal psychiatric background, and premorbid IQ < 85 predicted an early onset of FEP, as is described in Table 2. Figure 1 shows the adjusted probability prediction for EOP regarding the variables included in the logistic regression model.

DISCUSSION

Obstetric complications, a premorbid IQ < 85, and a personal background of psychiatric illness are all linked to EOP. Each of these characteristics was associated with a 4- to 5-fold increase in the probability of developing a first episode of psychosis before the age of 18 years. To our knowledge, this study is the first to look at early life factors and specifically link certain characteristics to the early onset of FEP rather than adult onset.

Studies comparing samples of early onset versus adult onset of schizophrenia or FEP are scarce considering the large number of articles that focus on this illness. Another problem is that, among the studies that have compared these two groups, widely different standards have been used to define early onset. While the generally accepted definition for this term is onset that occurs before the age of 18 years,[4] some studies have used other age thresholds (eg, younger than 40, 23, or 20 years[32–34]). Most of the studies analyzed symptoms at any point in the evolution of the disease, and some have found that premorbid adjustment is worse in patients with EOP than in those with AOP.[35–37] Using the PAS scale, we also found worse premorbid adjustment in EOS patients, and this grew even worse in the period preceding the onset of psychosis, as other authors have previously reported.[35–37] This difference is significant; however, because the changes tended to immediately precede the psychotic episode in our sample, PAS scale scores may not be particularly useful to give clinicians a head start to help prevent the early onset of FEP. In contrast, other early-stage factors that we studied could be effective for this purpose.

Obstetric complications have been consistently found to be an environmental risk indicator for schizophrenia.[38] A recent systematic review[12] associated OC with a 1.4- to 3.05-times higher risk of developing a psychotic disorder, depending on the specific type of complication. Interestingly, another systematic review[39] found that these complications were not consistently linked to the development of bipolar disorder compared to healthy controls, but they were associated with more frequent early onset of the disease (with cutoff ages for early onset set at 29 and 30 years, respectively[40,41]). Our data show that, among patients with FEP, those with any type of OC were 5.44 times more likely to have an early onset of the psychotic disorder, which is consistent with what had been described in a cohort of adult FEP patients.[42] In addition to their link to earlier onset, OCs have also been associated with greater morbidity.[11]

Prenatal and perinatal monitoring have improved in recent decades in most of the world. Studies comparing mothers who receive a standard number of prenatal visits (13–14) versus those who receive a reduced number of visits (4–9) have linked fewer visits with certain obstetric complications such as low birth weight or eclampsia.[43] However, fewer antenatal visits by mothers of offspring who later develop psychosis have been signaled as a possible reason for OCs.[12] Other factors such as increased maternal age could also affect this risk.[44,45]

Patients with any previous psychiatric diagnosis also had a 4-times greater risk of developing an EOP, which is consistent with the findings of other studies. For example, a study conducted in Denmark with data from the Danish nationwide register[46] found the risk of being diagnosed with a schizophrenia spectrum disorder before the age of 22 years was higher in subjects with any child and adolescent psychiatric diagnosis, especially in the first year after the onset of the disorder, and the incidence ratio more than 5 years after the diagnosis was 4.9 (95% CI, 4.37–5.54). Previous studies have also shown that being diagnosed with any psychiatric disorder during childhood or early adolescence is linked to developing schizophrenia spectrum disorders in adulthood.[47] This connection has been found to be particularly significant when there was a diagnosis of ADHD.[48,49] In our study, the model adjusted for logistic regression in the univariate analysis showed that there exists an association between having a previous ADHD diagnosis and EOP, but in the multivariate analysis this was not an independent predictor of EOP.

Premorbid intelligence measured with IQ has also been considered a risk factor for schizophrenia. In studies based on birth cohorts, individuals who later developed adult schizophrenia achieved lower scores on intelligence tests in childhood and adolescence than their peers.[50] A meta-analysis of population-based studies of premorbid intelligence and schizophrenia[13] confirmed that a significant reduction in premorbid IQ increased the risk of developing the disease. Specifically, it was reported that for every decrease of a single point in IQ, there was a 3.7% greater risk of developing the disease in adulthood. A similar level of increased risk was found in a large sample assessed in late adolescence and followed up for approximately 50 years.[51] That study associated the decrease of each point in IQ with a 3.8% greater risk of developing schizophrenia. Moreover, when age at illness onset was taken into account, there were more case-control differences in premorbid IQ in patients who had an earlier age at onset of schizophrenia.[13] Our data are consistent with previous findings in this area which have shown that patients with EOP had significantly lower IQ than those with AOP (with an approximate mean difference of 8 points). Additionally, subjects within the normal IQ range who had an overall IQ score < 85 had a higher risk of developing an EOP. This finding has not been previously reported. A possible explanation for this result could be that these individuals have a higher abnormal neurodevelopmental load or difficulties adjusting to problems, which may facilitate the appearance of symptoms.

Severe OCs have been associated with low cognitive functioning, while some such as preterm birth and intrauterine growth restriction have been linked to lower IQ in the general population.[52,53] In healthy controls, two co-occurring OCs have been associated with cognitive deficits, while in adult patients with schizophrenia, a single OC was linked to lower cognitive functioning compared to patients with no OC.[54] The exact relationship between OCs and low IQ is still unknown, but abnormal fetoplacental blood flow and hypoxia[52] might play a role in harming the developing brain.

Contrary to what might be expected, in our sample we found no association between an increased family history of psychosis and early versus adult onset of FEP. Familial genetic liability has been consistently found in early onset schizophrenia vs healthy controls[55,56] as well as versus adult-onset schizophrenia.[57] In a Danish study using nationwide registers conducted with twins,[58] it was found that early onset of the illness (< 18 years) in one of the twins was associated with an almost 7-times greater risk of the second twin's developing the disease. The authors of that study concluded that early onset of the illness could be a clinical marker for increased genetic vulnerability, suggesting that family background of psychosis may well play an important role in the early onset of schizophrenia and FEP, although we found no such link when examining our sample and comparing EOP patients with those who developed an adult onset of the disease.

The neurodevelopmental hypothesis of schizophrenia[9,10] and psychosis[59] and the developmental risk factor model[60] all posit that disruptions in normal brain development through fetal life, childhood, and adolescence are part of a process that leads to the disease. Certain detectable markers may indicate an individual's predisposition to develop psychosis, although environmental events may also play a role.[61] Studies such as those from the Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) consortium working groups[62] have found brain structural differences in EOP (low intracranial volume) and younger patients with clinical high risk (CHR) for psychosis (cortical

thickness disruptions in particular regions),[63] which suggest disrupted neurodevelopment in EOP and adolescent CHR. These findings show the importance of taking into account the neurodevelopmental phase when studying FEP.

Focusing on specific characteristics could help early intervention of psychosis programs more effectively delay or avoid the early onset of FEP.[64] We have found that early-stage factors such as OCs, personal psychiatric background, and IQ < 85 all predict an onset at < 18 years of age for the first episode of psychosis. Incorporating these findings into early intervention programs could be an effective tool to help prevent the onset of psychosis or limit its effects.

Limitations

There are several limitations to this study. The sample was reduced after it was divided into separate categories of EOP and AOP patients; ADHD was not systematically evaluated in the AOP sample since this diagnosis assessment is not included in the SCID-I, which we used; only patients' current treatments were recorded, and their use of stimulants to treat ADHD prior to the first episode of psychosis was not registered, although it has been reported that these could trigger psychotic disorders.[65] We did not assess other premorbid factors such as cognitive reserve, which may influence the age at onset.[66] Additionally, the information given by parents/legal tutors regarding child and adolescent patients may have been more reliable than information about adult patients because less time had gone by since the events had occurred.

Strengths

Among the strengths of this study is the fact that it examined an often overlooked distinction between EOP and AOP. The sample was relatively large and included a homogeneous and naturalistic population of subjects with FEP. Moreover, because subjects were prospectively recruited, the results can be more easily generalized. Finally, structured interviews and scales were used to increase the reliability of the data assessment.

Summary

In a sample of patients with FEP, several differences were found between subjects with early onset and those with adult onset. Obstetric complications, a previous psychiatric diagnosis, and an IQ < 85 were each linked to a 4- to 5-times increased risk of having FEP before age 18 years. Monitoring these early predictors of an EOP can help clinicians intervene to prevent the transition to psychosis in at-risk individuals. More research is needed in this key clinical field considering the significant repercussions of experiencing an EOP.

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