Duration of untreated psychosis predicts functional and clinical outcome in children and adolescents with first-episode psychosis: A 2-year longitudinal study

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ABSTRACT

Longer duration of untreated psychosis (DUP) in adult patients with first-episode psychosis (FEP) has been associated with poor clinical and social outcomes. We aimed to estimate the influence of DUP on outcome at 2-year follow-up in subjects with an early-onset (less than 18 years of age) FEP of less than 6 months’ duration. A total of 80 subjects (31.3% females, mean age 16.0 ± 1.8 years) were enrolled in the study. The influence of DUP on outcome was estimated using multiple regression models (two linear models for influence of DUP on the C-GAF at 2 years and C-GAF change through the follow-up period, and a logistic model for influence of DUP on 41 PANSS remission at 2 years in schizophrenia patients (n = 47)). Mean DUP was 65.3 ± 54.7 days. Median DUP was 49.5 days. For the whole sample (n = 80), DUP was the only variable significantly related to C-GAF score at 2-year follow-up (Beta = −0.13, p < 0.01), while DUP and premorbid adjustment (Beta = −0.01, p < 0.01; and Beta = −0.09, p = 0.04, respectively) were the only variables significantly related to C-GAF change. In schizophrenia patients, DUP predicted both C-GAF score at 2 years and C-GAF change, while in patients with affective psychosis (n = 22), DUP was unrelated to outcome. Lower baseline C-GAF score (OR = 0.91, p < 0.01) and shorter DUP (OR = 0.98, p = 0.09, p = 0.04) were the only variables that significantly predicted clinical remission in schizophrenia patients. In conclusion, longer DUP was associated with lower C-GAF at 2 years, less increase in C-GAF, and lower rates of clinical remission in early-onset FEP. Our findings support the importance of early detection programs, which help shorten DUP.

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1. Introduction

It has been shown that sociodemographic and clinical factors around the time of onset of illness, such as premorbid adjustment, insidious onset, and suicidal ideation, have significance for outcome in schizophrenia (Addington and Addington, 2008; Wunderink et al., 2009; Juola et al., 2013).

In addition, longer duration of untreated psychosis (DUP) in adult patients with first-episode psychosis (FEP) has been significantly associated with poor clinical and social outcomes (Larsen et al., 2000; Perkins et al., 2004, 2005; Harris et al., 2005; Marshall et al., 2005; Barnes et al., 2008; Schimmelmann et al., 2008; Wunderink et al., 2009; Cechnicki et al., 2011; Malla et al., 2011; Boonstra et al., 2012; Chang et al., 2012; Cuesta et al., 2012; Hill et al., 2012).

Mechanisms underlying the relationship between DUP and outcome are controversial (McGlashan, 1999; Rund, 2013). The TIP study found that reducing DUP was related to better course of symptoms and functioning over a two-year follow-up period (Melle et al., 2008). However, it is still not known whether untreated psychosis causes poorer prognosis per se, or whether subjects who are at risk for poor outcome (marked by poor premorbid adjustment) receive treatment long after the onset of symptoms, resulting in longer DUPs (Rund, 2013). In any event,
studies on this topic did not find a distinct association between DUP and clinical severity or functionality at baseline but did at follow-up (Marshall et al., 2005; Schimmelmann et al., 2008), which emphasizes the importance of early intervention, especially because DUP is a potentially modifiable prognostic factor (Perkins et al., 2005).

Early-onset psychosis (defined as psychotic disorder appearing before 18 years of age) has been associated with poor clinical and functional prognosis (Huber, 1997), and it has been shown that early detection and treatment of FEP are more effective in improving long-term functional outcomes in patients with early-onset schizophrenia than in those with adult-onset schizophrenia (Amminger et al., 2011).

However, although there is a study assessing DUP and outcome in a mixed sample (young adult and adolescent subjects, 15 to 25 years of age) (Chang et al., 2012), to our knowledge, there are no published studies on the relationship between DUP and clinical or functional outcome in early-onset FEP (less than 18 years of age). The aim of this study was to estimate the influence of DUP on functional and clinical outcome at 2-year follow-up in subjects with early-onset FEP.

On the basis of the previous literature on adults (Perkins et al., 2004, 2005; Marshall et al., 2005; Barnes et al., 2008; Schimmelmann et al., 2008; Hill et al., 2012), our initial hypothesis was that longer DUP would predict poor functional and clinical outcome in this pediatric FEP sample, given the relevant confounding factors, in particular premorbid adjustment.

2. Methods

2.1. Sample

The complete methods of the CAFEPS, a multicenter, longitudinal follow-up study of FEP in children and adolescents, have been comprehensively described elsewhere (Castro-Fornies et al., 2007). A sample of 110 patients (32.7% females) was consecutively recruited in outpatient and inpatient units at 6 hospitals in Spain. Recruitment took place between March 1, 2003 and November 31, 2005. Inclusion criteria were age between 7 and 17 years and a first episode of psychosis (positive symptoms) with a DUP of less than 6 months. A DUP of less than 6 months would avoid including most cases of psychosis with insidious onset, facilitating the evaluation of the influence of DUP on outcome.

The exclusion criteria were: 1) concomitant Axis I disorder at the time of evaluation, 2) mental retardation according to DSM-IV criteria, 3) any neurologic or pervasive developmental disorder, 4) history of head trauma with loss of consciousness, 5) pregnancy, and 6) substance abuse or dependence but not use if psychotic symptoms persisted 14 days after a negative urine drug test result. The study was approved by all institutional review boards at each clinical center, and written informed consent was obtained from all participants and/or their parents or legal guardians.

A subsample of 80 subjects (31.3% females) completed both the baseline and the 2-year follow-up functional and clinical evaluations, and composed this study sample. Fig. 1 shows the participant flowchart.

2.2. DUP

DUP was calculated as the time elapsed between the first positive symptom (delusions, hallucinations, or disorganization) recalled and baseline assessment. We used a clinical questionnaire to retrospectively monitor for date of onset of positive symptoms. To be considered a positive symptom as such, it was not necessary that it be accompanied by deterioration. The threshold was set as a symptom score of 3 or more on the PANSS. Sources of information included patient interview, clinical case notes, and questioning of the relatives and caregivers.

2.3. Diagnosis

Diagnosis was established according to DSM-IV criteria using the Spanish version of the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version, a semi-structured
diagnostic interview designed to assess current and past psycho-pathologic conditions (Kaufman et al., 1997; Soutullo, 1999). The interview was administered at baseline and follow-up. Parents and patients were interviewed separately by psychiatrists or clinical psychologists trained in the use of the instrument in children and adolescents. Diagnostic consensus was achieved for those patients in whom the type of a psychiatric disorder was in doubt. For data categorization, we used the final diagnosis established at the 2-year clinical follow-up assessment. Three main diagnostic categories were established: schizophrenia (41 patients with schizophrenia and 6 with schizoaffective disorder), affective psychoses (18 with bipolar disorder and 4 with depression with psychiatric features), and other psychoses (psychosis not otherwise specified in 5 subjects, and no longer meeting criteria for a psychiatric diagnosis at 2-year assessment in 6) (Castro-Forníes et al., 2011). Previous studies have reported shorter DUP in FEP patients diagnosed with bipolar disorder compared with those with schizophrenia (Schimmelmann et al., 2008). Therefore, statistical analyses should take this into account to avoid potential diagnosis-related confounding results.

2.4. Functional assessments

The child version of the Global Assessment of Functioning scale, Children’s Global Assessment of Functioning (C-GAF) scale (Shaffer et al., 1983), completed by the clinician, was used to assess psychosocial functioning.

The C-GAF is a numeric scale with a range of scores from 1 to 100. Scores above 70 are considered to be in the normal range. The Spanish version of the scale was used (Ézpeleta et al., 1999).

The physician completed this scale after the entire patient assessment visit was finished, based on his/her own clinical judgment and information given by the patient and his/her parents or legal guardians. Raters completed a training program on GAF assessment.

To estimate improvement or worsening in functionality through the 2-year follow-up, we calculate a C-GAF change score, as a proportion of C-GAF change: (C-GAF score at 2 years minus C-GAF score at baseline)/C-GAF at baseline.

Premorbid social adjustment was assessed at baseline using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) childhood subscale. In the PAS, items are measured with a Likert-type scale of 0 to 6, where lower values reflect better functioning.

2.5. Clinical assessments

Clinical assessment was performed at the corresponding clinical center by trained psychiatrists at different times. The rater was the same for each patient at baseline and 2-year follow-up. Severity of symptoms was measured using the Spanish validated version of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Peralta Martín and Cuesta Zorita, 1994). Interrater reliability for the PANSS was determined using the intraclass correlation coefficient, which was higher than 0.80 for all subscales and total score. Symptomatic remission was assessed in the subsample of patients with schizophrenia (n = 47) using the standardized remission criteria in schizophrenia, i.e., score of 3 or less on all of the following PANSS items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), mannerisms/posturing (G5), unusual thought content (G8), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and flow of conversation (N6) (Andreasen et al., 2005; van Os et al., 2006).

Vocabulary and block design subtests of the Wechsler Intelligence Scale for Children or the Wechsler Adult Intelligence Scale were used to estimate the intelligence quotient (IQ) of those younger than 16 years or 16 years and older, respectively (Satler, 2001). The subtests were administered by experienced neuropsychologists trained in the use of these instruments. Interrater reliability, determined using the intraclass correlation coefficient, ranged from 0.80 to 0.99 in all cases.

2.7. Statistical analyses

For univariate analyses, continuous variables were assessed using ANOVA analyses and the Pearson product-moment correlation coefficient; both after checking the linear model assumptions (Kolmogorov–Smirnov and Shapiro–Wilks tests were assessed). Qualitative variables were studied with a chi-squared test.

Two multivariable linear regression models and a multivariable logistic regression model were used to study the independent value of predictor variables and their interactions (after checking the model assumptions and studying the correct adjusted model). Results are presented as adjusted risk ratios with 95% confidence intervals. No significant first-order interactions were found in the models.

In particular, to estimate the influence of DUP on the C-GAF at the 2-year follow-up and C-GAF change, two multiple linear regression models were used, including as independent variables (based on previous literature): DUP (Perkins et al., 2004, 2005; Marshall et al., 2005; Addington and Addington, 2008; Barnes et al., 2008; Schimmelmann et al., 2008; Hill et al., 2012), C-GAF at baseline (except for C-GAF change as a dependent variable), age (Huber, 1997; Amminger et al., 2011; Juola et al., 2013), gender (Wunderink et al., 2009), baseline total PANSS score (Wunderink et al., 2009; Schennach-Wolf et al., 2011), cumulative antipsychotic doses (chlorpromazine equivalents) (Emsley et al., 2007), PAS score (Larsen et al., 2000; Verdoux et al., 2001; Addington and Addington, 2008; Jeppesen et al., 2008), IQ (Leeson et al., 2009), diagnostic group (Schimmelmann et al., 2008; Wunderink et al., 2009; Schottle et al., 2012), manic episode at baseline (because patients with mania at baseline had shorter DUP than non-manic patients, 32.56 (31.68) vs. 69.41 (55.77) days, p = 0.010), and interactions between the above factors. We repeated the analyses for the independent diagnostic groups separately and after taking diagnosis out of the model.

To estimate the influence of DUP on PANSS remission at 2 years in schizophrenia (Andreasen et al., 2005; van Os et al., 2006), a logistic regression analysis was performed on the group of patients with schizophrenia (n = 47) using all the aforementioned variables, with the exception of diagnosis and manic episode at baseline, as independent factors.

To validate the logistic regression, we performed an ROC analysis, obtaining a sensitivity of 78.8% and a specificity of 76.0%.

A correction for multiple comparisons was not done because there was no data mining, all regression analyses were independent, the between-group comparisons were established ‘a priori,’ and all regression assumptions (variables are continuous, the relationship between the variables is linear, there are not significant outliers, the observations are independent, variables show homoscedasticity, and residuals have a normal distribution) were checked (Gelman et al., 2012). Effect sizes and confidence intervals are shown for all regression analyses (Johnson, 1999).

The level of significance was set at p < 0.05. All statistical tests were two-tailed using SPSS software for Windows version 18.0.

3. Results

Sociodemographic variables are shown in Table 1. No sociodemographic or clinical differences (age, gender, total PANSS score at baseline, C-GAF at baseline, or IQ) were found between the
patients who completed the follow-up (n = 80) and those who did not (n = 30).

Regarding the relationship between DUP, PAS, and C-GAF at baseline, we found that the shorter the DUP, the lower the functional achievement at baseline (lower C-GAF) (r = 0.297, p = 0.007), while the correlation between PAS and C-GAF at baseline was not significant (r = 0.134, p = 0.236). The correlation between DUP and PAS showed that longer DUP was modestly associated with poor premorbid adjustment (higher PAS) (r = 0.221, p = 0.049, n = 80). Partial correlation between DUP and C-GAF at baseline, after controlling for PAS, showed a significant relationship (r = 0.276, p = 0.014).

Results of the significant independent variables associated with the outcome variables for the whole group and by diagnostic group are presented in Table 1.

3.1. Relationship between DUP and C-GAF at 2-year follow-up

For the whole sample, the bivariate correlation between DUP and C-GAF at 2 years was r = −0.379, p = 0.001. In schizophrenia patients, it was r = −0.384, p = 0.008. In the subsample of patients with affective psychosis, the correlation between DUP and C-GAF at 2 years was not significant (r = −0.124, p = 0.583).

The multiple linear regression model showed that, for the whole sample (n = 80), DUP (p = 0.001) was the only variable significantly related to C-GAF score at 2-year follow-up.

In schizophrenia patients (n = 47), DUP (p = 0.008) was the only variable significantly related to C-GAF score at 2 years, while in patients with affective psychosis (n = 22), none of the studied variables used in the multiple regression model were significantly related to C-GAF score at 2 years, while in patients with affective psychosis (n = 22), none of the studied variables used in the multiple regression model were significantly related to C-GAF change.

Table 2 shows the regression models.

3.2. Relationship between DUP and C-GAF change through the 2-year follow-up

For the whole sample (n = 80), the bivariate correlation between DUP and C-GAF change was r = −0.380, p = 0.001. In schizophrenia patients (n = 47), it was r = −0.349, p = 0.016, whereas in patients with affective psychosis (n = 22), it was r = −0.436, p = 0.042.

Bivariate correlations between DUP and both C-GAF at 2 years and C-GAF change are shown in Fig. 2.

The multiple linear regression model showed that, for the whole sample (n = 80), DUP (p = 0.027) and premorbid adjustment (p = 0.041) were the only variables significantly related to C-GAF change. By diagnostic group, factors significantly associated with C-GAF change were: DUP (p = 0.027) and premorbid adjustment (p = 0.020).
4. Discussion

In this 2-year longitudinal study in patients with early-onset FEP, longer DUP was associated with poor functional and clinical outcome. In particular, longer DUP predicted both lower C-GAF score at 2-year follow-up and less increase in C-GAF through the follow-up period. In the subsample of patients with schizophrenia, longer DUP was associated with lower rates of PANSS remission at 2-year follow-up.

To our knowledge, this is the first prospective study of an inception cohort of early-onset FEP patients that has examined the effect of DUP on functional and clinical outcome.

4.1. Nature of the relationship between DUP and outcome

Two systematic reviews have previously demonstrated that DUP is an independent predictor of the likelihood of recovery in FEP patients (Marshall et al., 2005; Perkins et al., 2005). However, the nature of the association between DUP and outcome is still controversial. Is there a causal pathway linking longer DUP and poor outcome? Or, conversely, is the relationship between DUP and outcome spurious, finding with no direct causal link between these variables? These questions have led to the formulation of different hypotheses about the relationship between DUP and outcome (McGlashan, 1999; Perkins et al., 2005).

The relationship between DUP and outcome may be confounded by insidious onset (Morgan et al., 2006). In line with the notion of
a) Bivariate correlations between DUP and C-GAF at 2 yrs in the whole sample (n=80)

b) Bivariate correlations between DUP and change in C-GAF in the whole sample (n=80)
psychosis as a complex and multidimensional syndrome (van Os et al., 2010), patients with a more insidious form of onset, and, accordingly, with longer DUP, could represent the poor outcome fraction of the psychotic syndrome, with poor cognitive, clinical, and social prognosis. In this hypothetical case, the relationship between DUP and poor outcome would be spurious, and longer DUP would just represent an epiphenomenon of an underlying pathophysiological factor (Verdoux et al., 2001). Some studies that have included both insidious onset and DUP as independent predictive factors have found type of onset rather than DUP to be more relevant to outcome (Ropcke and Eggers, 2005; Penttila et al., 2013). However, mean DUP in these studies was longer than 200 days (Ropcke and Eggers, 2005; Penttila et al., 2013), so the relative weight of insidious onset was very high, limiting the effect of DUP on clinical and functional outcome. This is especially relevant because both longer DUP and insidious onset may be independent predictors of poor outcome (Wiersma et al., 1998), confounding the findings on the relationship between DUP and outcome. This could have been the case in studies with very long DUP (Ropcke and Eggers, 2005; Penttila et al., 2013). For this reason, our sample of FEP patients with positive symptoms for less than 6 months of (mean DUP (SD) 65.26 (54.73) days, range 1–180 days) provides a better scenario to study the independent influence of DUP on outcome. This is particularly relevant because DUP in adolescent-onset psychosis has been found to be longer than DUP in adults (Dominguez et al., 2013).

The relationship between DUP and outcome may also be confounded by premorbid adjustment (Larsen et al., 2000, 2004). In keeping with previous findings (Verdoux et al., 2001; Jeppesen et al., 2008), we found that longer DUP was modestly associated with poor premorbid adjustment (r = 0.221, p = 0.049, n = 80). Based on these data, it could be hypothesized that premorbid adjustment is independently associated with both DUP and outcome, with no causal link between these two latter variables. But then, it also could be posited that DUP is on the causal pathway between premorbid adjustment and outcome (Verdoux et al., 2001). In any case, longer DUP has been found to be related to poor premorbid adjustment, and poor premorbid adjustment is a risk factor for late detection of psychosis, possibly because it delays help-seeking (Morgan et al., 2006). In our study, we found an intriguing relationship between DUP and baseline C-GAF score, i.e., the shorter the DUP, the lower the functional achievement at baseline (r = 0.297, p = 0.007), while premorbid adjustment was unrelated to C-GAF score at baseline (r = 0.134, p = 0.236). Correlations between longer DUP and both poor premorbid adjustment and better functionality are compatible and have a plausible clinical explanation in that it would be expected that young people with more severe acute psychopathology seek help (mainly through their parents) earlier those with less severe psychopathology, independently of premorbid adjustment (partial correlation between DUP and C-GAF at baseline, controlling for PAS: r = 0.276, p = 0.014).

4.2. Lower baseline C-GAF score significantly predicted PANSS remission in schizophrenia patients

We found that lower baseline C-GAF score significantly predicted PANSS remission, which may be counterintuitive. This was an unexpected result, as previous studies in adult subjects with FEP have reported that symptomatic recovery is significantly associated with short DUP and better baseline functioning (Wunderink et al., 2009). However, methodological differences may explain the apparent contradictory results. Although at first sight a lower GAF score may be interpreted as a more severe situation, it does not necessarily reflect more a severe psychotic disorder but rather a more maladjusted status. The sample analyzed in this study was recruited from 83.6% of the cases at the time of admission for a first psychotic episode (Castro-Fornieles et al., 2007) and a lower GAF may reflect an overt behavioral disturbance (e.g., more aggressive behavior). In fact, neither the baseline positive nor the negative subscales of the PANSS contributed to 2-year remission status in this sample, therefore it is not the severity of symptoms that is predicting remission. In the Wunderink study, patients were recruited after acute symptoms resolved and therefore baseline functioning was not affected by acute decompensation. Our study design does not allow us to reach a definite conclusion regarding this result. However, we can speculate that, in our early-onset FEP sample, the relationship between lower baseline C-GAF and higher PANSS remission rates may be confounded by DUP. We found that short DUP was related to worse baseline functioning. Therefore, as we pointed out in the previous section, adolescent patients with worse functioning would seek help (principally through their parents) earlier than those with better functioning, resulting in shorter DUP.

4.3. DUP and outcome were related in patients with schizophrenia but not in those with affective psychosis

Our results showed that relationships between DUP and both C-GAF at 2 year follow-up and C-GAF change were significant in subjects with schizophrenia, but not in those with affective psychosis. This finding may, at least in part, be attributed to the differences in DUP between diagnostic groups: DUP is shorter in patients with affective psychosis than in those with schizophrenia (mean ± SD 48.50 ± 48.83 vs. 77.96 ± 54.55, p = 0.034). This result is concordant with previous reports on shorter DUP in FEP patients diagnosed with bipolar disorder compared with FEP schizophrenia or schizoaffective patients (Schimmelmann et al., 2008; Schottle et al., 2012). In our sample, 9 out of 22 subjects with affective psychosis were enrolled after a manic episode, and patients with a manic episode at baseline had short DUP (mean ± SD 32.56 ± 31.66 days), suggesting that they seek help earlier.

The same result, i.e., lack of relationship between DUP and both C-GAF at 2-year follow-up and C-GAF change, was also found in the subsample of patients with bipolar disorder (n = 18).

Therefore, it is plausible that the smaller range of DUP in patients with a manic episode (range 4–95 days versus 1–180 days in the whole sample) precludes finding a significant relationship between DUP and outcome. However, the regression analyses were controlled for mania at baseline (as dichotomous yes/no variables). This result in affective psychosismay also be due to specific pathophysiological conditions. It has been reported that schizophrenia and bipolar disorder share similarities and dissimilarities in neurodevelopment trajectories (Arango et al., in press). So it could be proposed, as one possible underlying mechanism, that trajectories of patients with affective psychosis are less prone to be modified with early intervention than those of subjects with schizophrenia. Of course, this statement needs empirical validation.

4.4. Strength and weaknesses

The key strength of the study was longitudinal assessment of patients with early-onset FEP. Our FEP sample with less than 6 months of positive symptoms does not include most of the forms of psychosis with insidious onset, facilitating the evaluation of the influence of DUP on outcome.

This study has also some weaknesses. Firstly, DUP was calculated as the time elapsed between the first positive symptom recalled and the baseline assessment, and no standardized scale was used to assess it. All 80 patients had a DUP shorter than 6 months (range 1–180 days). Although this represents a limitation, it should be borne in mind that, in acute onset, it is possible to determine the time of onset with greater precision than in insidious onset of illness. In general, studies assessing DUP have an inherent limitation due to absence of standardized criteria for defining DUP (Compton et al., 2007). Secondly, the other psychoses diagnostic group is a heterogeneous cluster that includes different disorders with different outcomes. Thirdly, the GAF was introduced as a rating scale to assess
psychological, social, and occupational functioning on a hypothetical continuum of mental health–illness (American Psychiatric Association, 2000). The GAF has been shown to reflect the construct of global functioning that it was designed to measure (Schwartz, 2007). However, the GAF scale has some limitations that deserve to be stated. The GAF integrates three different dimensions of functioning (i.e., social, occupational, and psychological symptoms) that do not necessarily covary (Roy-Byrne et al., 1996; Pedersen and Karterud, 2012). Furthermore, although the GAF is assessed on a hypothetical continuum and, in our sample, follows normal distribution (Kolmogorov–Smirnov Z: 1.355, p = 0.051), it does not mean that GAF score is a valid quantitative measure. In fact, GAF scale has marked similarities with categorical scales and, to some extent, acts as a categorical or discrete scale (as it is divided into 10 categories, the difference between 80 and 60 points is clinically equivalent to the difference between 40 and 20) (Aas, 2010). Moreover, GAF scores are primarily sensitive to variation in clinical symptom severity but less sensitive to variation in social cognition (Robertson et al., 2013). Fourthly, raters completed a training program on GAF assessment. However, reliability was not tested. Finally, it is worth noting that the methodology of this study does not allow for inference of a causal relationship between DUP and outcome. We cannot confirm whether the association we found is causal in nature or if it is mediated by another underlying variable.

4.5. Clinical implications and future directions

Our finding on the association between longer DUP and poor functional and clinical outcome in early-onset FEP highlights the importance of going beyond the mere relationship and finding out the underlying nature of this association (Perkins et al., 2005; Rund, 2013). In any case, our results support the value of early detection programs, which help shorten DUP (Larsen et al., 2001). Recent findings from longitudinal studies advocate that schizophrenia should not be conceived as an inevitably deteriorating disease (Zipursky et al., 2013). Given that DUP constitutes a potentially modifiable time window, our results support the value of early detection programs, which are primarily sensitive to variation in clinical symptom severity but less sensitive to variation in social cognition (Robertson et al., 2013). Fourthly, raters completed a training program on GAF assessment. However, reliability was not tested. Finally, it is worth noting that the methodology of this study does not allow for inference of a causal relationship between DUP and outcome. We cannot confirm whether the association we found is causal in nature or if it is mediated by another underlying variable.

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Contributors

Celso Arango, Josefina Castro-Fornieles, Soraya Otero, Ana Gonzalez-Pinto, Immaculada Baeza, Dolores Moreno, Celso Arango and Mara Parellada designed the study and wrote the protocol. David Fraguas, Ángel del Rey-Mejías, Mónica Martínez-Cengotitabengoa, Celso Arango and Mara Parellada, managed the literature searches and analyses. David Fraguas, Ángel del Rey-Mejías and Mara Parellada undertook the statistical analysis. David Fraguas wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Fraguas has been a consultant and/or advisor to or has received honoraria from Astra-Zeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Otsuka, Pfizer, Sanofi-Aventis, Servier, Schering-Plough, Solvay, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, the Stanley Medical Research Institute, and Wyeth. Dr. Dolores Moreno reports no competing interests. Dr. Inmaculada Baeza has received honoraria from Otsuka. Dr. Mónica Martínez-Cengotitabengoa reports no conflict of interest. Dr. Arango has been a consultant to or has received honoraria or grants from Abbot, AMC/GEN, Astra-Zeneca, Bristol-Myers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Instituto de Salud Carlos III, Janssen Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Pfizer, Roche, Servier, Shire, Takeda and Schering Plough. Dra. Parellada reports no conflict of interest. There are no other published data or manuscripts based on these data pending a decision.

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