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Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10 year follow-up study in the OPUS cohort

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ABSTRACT

Objective: Knowledge about course of illness can help clinicians to develop effective interventions and improve treatment outcomes. The goal of this study was to construct positive and negative symptom trajectories based on structured clinical assessments collected over 10 years within a cohort of people with first episode psychosis.
Method: A cohort of 496 people with first episode psychosis (ICD-10, F20-28) originally recruited for the OPUS study (1998–2000) and treated in community psychiatric services were rated on clinical symptoms at 5 different occasions across ten years. Psychopathology was assessed using the Scales for Assessment of Positive and Negative Symptoms. Symptom trajectories were constructed using Latent Class Analysis.
Results: Five distinct trajectories were identified for positive symptoms (response — 47%, delayed response — 12%, relapse — 15%, non-response — 13% and episodic response — 13%). Four distinct trajectories were identified for negative symptoms (response — 28%, delayed response — 19%, relapse — 26% and non-response — 27%). Multivariable regression analysis of baseline characteristics identified that longer duration of untreated psychosis (OR 1.27–1.47, $p < 0.05$) and substance abuse (OR 3.47–5.90, $p < 0.01$) were associated with poorer positive symptom trajectories (higher levels of psychotic symptoms) while poor social functioning (OR 1.34–5.55, $p < 0.05$), disorganized symptoms (OR 2.01–2.38, $p < 0.05$) and schizophrenia diagnosis (OR 5.70–8.86, $p < 0.05$) were associated with poorer negative symptom trajectories (higher levels of negative symptoms). A proportion of people displayed significant changes in symptoms several years after diagnosis.
Conclusions: Trajectories of illness for positive and negative symptoms were heterogeneous among people with first episode psychosis. Positive symptoms showed a general pattern of reduction and stabilization over time while negative symptoms typically showed less variation over the ten years. Results have implications for the focus, timing and length of interventions in first episode psychosis.

1. Introduction

The investigation of long-term outcomes is a key focus within schizophrenia research. Information on long term prognosis can assist in the identification of factors that could impact on illness course. While it has been previously proposed that the typical course of illness in schizophrenia is chronic and deteriorating (Davidson and McGlashan, 1997), recent studies have indicated that a heterogeneous course of illness is most characteristic, with a significant number of people achieving symptom remission and recovery (Van Os and Kapur, 2009; Henry et al., 2010a; Harrow et al., 2005; Wunderink et al., 2009).

Traditionally, long-term outcomes in schizophrenia have been assessed by investigating the rates of symptom remission and recovery at a specified time after diagnosis (Menezes et al., 2006). While these studies provide valuable cross sectional information about levels of psychopathology and functioning for people with schizophrenia, they do not provide detailed information about how the illness is manifested over time. Studies using longitudinal data can contribute to a better understanding of the course of illness and help clinicians to adjust the timing and intensity of interventions to optimize treatment outcomes for people with schizophrenia.

The classification of outcomes into dichotomous categories such as recovered or not and symptom remission or not, is commonplace within schizophrenia research but this practice can also be problematic. If dichotomization is undertaken without evidence of a bimodal distribution, this may lead to the inefficient analysis of continuous data, where up to one third of the data from the sample is thrown away (Streiner, 2002; Royston et al., 2006). Furthermore, cut-off scores for membership into a particular category are often arbitrary in nature (Mulder et al., 2003). The oversimplification of complex outcomes into

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categories such as recovered/not recovered can create difficulties in the translation of results into clinically meaning information (Rietschel et al., 1999).

Advances in statistical modeling techniques have meant that it is now possible to identify categories based on temporal patterns of change using latent class models (LCA) and growth mixture modeling (GMM) (Beunckens et al., 2008). The advantage of these methods is that the subpopulations and thresholds do not need to be defined or identified arbitrarily. Furthermore, LCA and GMM are sensitive to the pattern of change over time and are robust in the presence of missing data (Muthen et al., 2002; Muthen and Brown, 2009).

Recently, a number of studies have used LCA or similar growth mixture models to identify different trajectories to treatment response within schizophrenia. Rabinowitz and colleagues identified three response trajectories within a cohort of people with schizophrenia over a period of ten years. A significant majority showed improvement and stabilization in positive symptoms (Rabinowitz et al., 2007). Levine et al. (2011) identified five distinct illness trajectories, where the typical course was one of initial deterioration followed by progressive amelioration (Levine et al., 2011). A limitation of both these studies was the use of number of days hospitalized as a proxy for clinical symptoms, which may not directly reflect levels of psychopathology, given the criteria for admission to hospital can vary depending on the health service.

A number of studies have identified trajectories based on clinical ratings of positive symptoms. Schennach et al. (2012) identified five response trajectories, where the majority of participants showed a moderate to good response (Schennach et al., 2012) while Case et al. (2010) identified four trajectories with over 80% of participants displaying a pattern of gradual improvement within the first three months of treatment (Case et al., 2010). The results from these studies were limited due to the very short follow-up period (12 weeks), given that schizophrenia is an illness manifested over several years. While these modern statistical techniques are generating new information about symptom trajectories in schizophrenia, further longitudinal studies using clinical data are required. Furthermore, there are no current studies that have examined negative symptom trajectories using clinical data and latent class analysis.

The aim of this study was to identify discrete trajectories for positive and negative symptoms using structured clinical assessments collected over a ten year period within a large representative sample of people with first episode psychosis. Additionally, the study identified which baseline characteristics discriminated between different trajectories.

2. Method

2.1. Sample

A sample of 496 patients who received ICD-10 diagnosis of schizophrenia spectrum disorder diagnosis (F20–29) were recruited in the original OPUS trial (1998–2000). People with a schizotypal disorder (F21) were excluded, as the study was concerned with identifying symptom trajectories for people that had experienced psychotic symptoms at the time of inclusion. None of the participants recruited for the OPUS trial had received more than 12 weeks of anti-psychotic medication. The original OPUS study was a randomized control trial that investigated the effect of two different treatments: specialized assertive early treatment and standard outpatient treatment. The specialized assertive treatment comprised of three key elements: assertive community treatment, family psychoeducation and social skills training. Results collected after two years of treatment revealed that those who had received the specialized assertive intervention displayed significantly less symptoms and better functioning compared to those in the standard outpatient treatment. All patients reverted back to standard treatment after the two years. All participants were invited to participate in a five and ten year follow-up after inclusion in the study. Participants were contacted using the personal identification number (CPR), which all Danish residents are assigned. This number provides access to a person's contact details including current address and utilization of health services. At five year and ten year follow-up there were no differences between the two treatments on the primary outcomes (symptoms and functioning). A detailed description of the treatments, study design and results from the OPUS trial have been previously published (Bertelsen et al., 2008; Petersen et al., 2005; Secher et al., 2014). All participants provided written informed consent regarding their participation in this research study.

A pragmatic decision to combine the two treatment groups into a single FEP cohort was made, as there were no differences between treatment condition at 5 and 10 year follow-up. Examining trajectories in the entire cohort increased the statistical power of the analyses and generalizability of the findings. Treatment type (assertive treatment and standard treatment) was included as a covariate in the analysis of factors that impact on trajectories. Thus, it was possible to determine the specific effect of treatment type on the trajectories identified.

2.2. Design and measures

This study utilized clinical data on positive and negative symptoms collected at five different time points throughout the ten year period (baseline, 1 year, 2 years, 5 years and 10 years).

Psychopathology was assessed at all time points with the Scales for Assessment of Positive (SAPS) and Negative Symptoms (SANS) (Andreasen et al., 2005; Arndt et al., 1995). A composite score using global scores for SAPS and SANS was calculated to provide a single continuous measure for psychotic symptoms and negative symptoms, respectively (Arndt et al., 1995). Both SAPS and SANS evaluated the severity of symptoms on a 6 point Likert scale (from 0 — absent through to 5 — severe). A symptom score of 3 and over was deemed clinical significant. The disorganization dimension of psychopathology was examined using SAPS. Variation in this symptom dimension was minimal where symptom levels ranged from absent to mild (0–2 on a 6 point scale) over the 10 year period. Thus, it was not deemed feasible to identify different trajectories in this dataset and this symptom dimension was not included in the analysis.

Level of functioning was evaluated by the Global Assessment of Functioning scale (GAF) (American Psychiatric Association, 1994), divided into functioning (GAF-F) and symptoms (GAF-S) (Pedersen et al., 2007). Pre-morbid functioning at baseline was assessed using the Pre-morbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), with a higher score indicating poorer functioning. Duration of untreated psychosis was assessed at baseline using the Interview for Retrospective Assessment of Onset of Schizophrenia (IRAOS) (Hafner et al., 1992). DUP was defined as the time period with at least one psychotic symptom definitely present until the initiation of treatment (Jeppesen et al., 2008). Other baseline characteristics such as substance abuse, social contact and disorganized symptoms were measured using ICD-10, the Strauss Carpenter Scale and SAPS (World Health Organisation, 1993; Strauss and Carpenter, 1972; Arndt et al., 1995; Andreasen et al., 1990).

Systematic training and rating using the SAPS and SANS was undertaken throughout the assessment period. Calculation of the intra-class correlation coefficient (ICC) for the assessors at different follow-up points ranged from 0.77 to 0.92 for SAPS and 0.54 to 0.90 for SANS which corresponds moderate to very good agreement (Bartko and Carpenter, 1976). Assessors were blind to treatment condition at follow-up assessments.

2.3. Statistical analysis

This study used latent class analysis (LCA) to identify distinct groups or trajectories for positive and negative symptoms over a period of 10 years. A trajectory is a group of people that have a homogenous symptom profile within that group and significantly

dissimilar (i.e., heterogeneous) from other groups (Levine and Leucht, 2010). For each person LCA uses outcomes at all time points to enable estimation of the probability of belonging to each of the identified groups. The results included an estimated symptom profile for each latent class.

The optimal number of trajectories was identified by using the Bayesian Information Criterion (BIC) to ensure parsimony (Raferty, 1995). Thus, the estimation process started with a 2 class model and kept increasing the number of classes until there was an increase in the BIC-value.

Patients with incomplete symptom data were included in the analysis by assuming values are missing at random (Little and Rubin, 1987). This approach is standard when analyzing longitudinal data as it in contrast to a complete case analysis does not assume that the missing values are a random subset. The risk of having a missing value is allowed to depend on variables that are observed. In the current data, we have almost complete information on covariates and baseline variables. Therefore our analysis will be unbiased as long as the risk of having a missing value can be predicted based on these variables.

In order to determine which baseline characteristics discriminated between trajectories a two-step analysis was employed. In the first step univariable logistic regressions were conducted (response trajectory was used as the reference category) to identify which variables separately contributed individual trajectories. The baseline variables investigated were: gender, pre-morbid academic and social functioning, amount of social contact, substance abuse, age of onset for illness, current functioning, duration of untreated psychosis, negative symptoms, positive symptoms, disorganized symptoms, schizophrenia diagnosis, type of treatment (assertive or standard) and completion of high school. The second step in the analysis involved putting all the significant univariable predictors ($p < 0.05$) into a multivariable analysis to identify which of these predictors still predicted different trajectories when accounting for the shared variance between variables. Significant predictors for the multivariable model were identified using a stepwise backwards elimination process. As the cohort of people received different treatments within the first two years (standard versus intensive assertive), treatment was also entered as a covariate in the multivariable predictor analysis for positive and negative symptom trajectories.

A number of these baseline variables were recoded for ease of interpretation. A point increase in DUP equated to a 1 year increase in DUP, a point increase on pre-morbid social or academic functioning equated to a 10% reduction in premorbid functioning, a point increase on GAF-F equated to a 10% increase in functioning and a one point increase on age of onset equated to 10 years older. The statistical package used in this analysis was Mplus, version 7 (Muthen and Muthen, 2012).

3. Results

The baseline characteristics of the sample (n = 496) are presented in Table 1. The majority of participants had a schizophrenia diagnosis (F20). Mean age was approximately 27 years at inclusion and a third of the sample had a substance abuse diagnosis at baseline. A total of 446 people participated at 1 year follow-up, 406 people participated at 2 year follow-up, 265 people participated at 5 year follow up and 304 people participated at 10 year follow-up. There were no significant differences between participators and non-participators on baseline characteristics at 1, 2 or 5 year follow-up (Bertelsen et al., 2008). At 10 year follow-up participators scored higher on global functioning (GAF-F) (mean = 41.20, S.D. = 11.97) than non-participators (mean = 37.55, S.D. = 13.68, t (483) = 2.98, p = 0.003) and participators were younger (mean age. = 26.18 years, S.D. = 6.33) compared than non-participators (mean = 27.59, S.D. = 6.66, t (492) = 2.37, p = 0.018) at baseline (Austin et al., 2013).

Fig. 1 contains the results of the latent class analysis for positive symptoms. For positive symptoms five distinct trajectories were identified as the optimal fit for the data (BIC: 3 classes 5901, 4 classes 5823, 5 classes 5804, 6 classes 5814). The *response trajectory* (47%, n = 233) was characterized by a significant reduction in symptoms within the first year followed by maintenance over the remaining years. The *relapse trajectory* (15%, n = 75) displayed a relapsing response pattern where there was an initial reduction in symptoms within the first two years followed by a steady increase over the remaining eight years. The *delayed response trajectory* (12%, n = 60) showed an initial decrease, then increase in symptoms within the first two years followed by a steady decrease over the remaining eight years. The *no response trajectory* (13%, n = 64) displayed significant positive symptoms throughout the entire follow-up period. The remaining 13% (n = 64) displayed an initial decrease in positive symptoms followed by increase then subsequent decrease over the 10 years and were classified as the *episodic response trajectory*.

Table 1
Baseline characteristics of OPUS sample (n = 496).

Characteristic	Percentage or raw scores (number or S.D.)
Male (n)	57.7% (n = 285)
Mean age at inclusion in trial (S.D.)	26.7 years (6.49)
Diagnosis (ICD 10 criteria) — percentage of sample (number)	
Schizophrenia	78.2% (n = 388)
Delusional disorder	5.2% (n = 26)
Acute psychosis	9.3% (n = 46)
Schizoaffective disorder	5.1% (n = 25)
Unspecified psychosis	2.2% (n = 11)
Treatment condition	Assertive treatment (n = 261) Standard treatment (n = 235)
Psychopathology (SAPS/SANS) — mean (S.D.)	
Psychotic dimension	3.00 (1.32)
Negative dimension	2.21 (1.16)
Disorganized dimension	1.06 (0.96)
Duration of untreated psychosis (DUP) — median in weeks	52.00
Global Assessment of Functioning (GAF) — mean (S.D.)	
GAF-S symptoms	31.34 (9.69)
GAF-F functioning	39.77 (13.15)
Substance abuse diagnosis — percentage of sample (number)	29% (n = 144)

Results from the analysis for negative symptoms identified four distinct trajectories (Fig. 2) as the optimal fit for the data (BIC: 3 classes 5176.63, 4 classes 5153.63, 5 classes 5154.28). The *response trajectory* (28%, n = 139) was characterized by a reduction of negative symptoms over the first two years followed by stabilization. The *no response trajectory* (27%, n = 134) displayed stabile and moderate levels of negative symptoms throughout the ten year follow-up period. The *relapse trajectory* (26%, n = 129) showed a slight reduction in negative symptoms during the first two years followed by a steady increase over the remaining eight years where symptoms returned to baseline levels. The remaining 19% (n = 94) displayed a *delayed response trajectory* with an initial increase in symptoms in the first two years followed by gradual decrease to minimal levels throughout the remaining eight years.

A univariable multinomial logistic regression analysis identified which baseline characteristics were associated with different positive symptom trajectories. Significant variables from these analyses were placed in a multivariable model (Table 2). Longer DUP, substance abuse, schizophrenia diagnosis and poorer functioning at baseline were associated with different positive symptom trajectories. Treatment received within the first two years (assertive vs. standard) was not a significant predictor for any of the positive symptom trajectories over the 10 years.

Gender, pre-morbid academic functioning, baseline negative symptoms and completion of high school were not significant predictors in the multivariable analysis for any of the positive symptom trajectories and not included in Table 2.

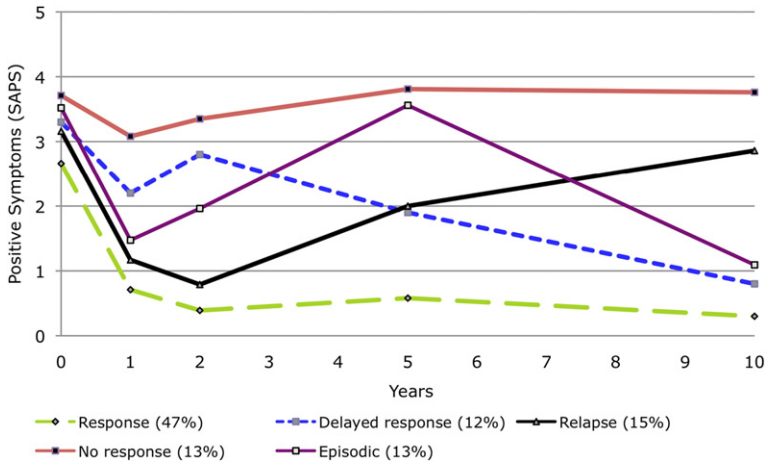

Fig. 1. Positive symptom trajectories for 10 year period (SAPS scoring: 0 — absent, 1 — questionable, 2 — mild, 3 — moderate, 4 — marked, 5 — severe).

Significant results from the univariable analysis for negative symptom trajectories were placed into the multivariable model, where male gender, poor pre-morbid or inadequate social functioning, schizophrenia diagnosis, higher global functioning and disorganized symptoms discriminated between different negative symptom trajectories (Table 3). Treatment received within the first two years did impact on one specific negative symptom trajectory, where people receiving standard treatment were more likely to display a delayed symptom trajectory compared to those participating in the assertive intervention (OR 6.03, $p = 0.01$). Gender, pre-morbid academic functioning, DUP, baseline negative symptoms and completion of high school were not significant predictors for any of the negative symptom trajectories in the multivariable analysis and these variables are not included in Table 3.

4. Discussion

This study investigated long-term trajectories in first episode psychosis and continues the body of research that has examined the manifestation of psychopathology over time (Goghari et al., 2013; Harrow et al., 1997; Herbener and Harrow, 2001, 2004) using statistical techniques to identify symptom course based on longitudinal clinical data. Results indicate that the majority of participants experience a reduction and stabilization of positive symptoms over time while changes in negative symptoms were not as marked, with over half the participants showing no major changes from baseline levels. A number of baseline characteristics significantly discriminated between different trajectories.

4.1. Positive symptom trajectories

Results support a heterogeneous course for positive symptoms with five distinct trajectories identified within the cohort. For positive symptoms, a pattern of reduction followed by stabilization is displayed in 59% of the sample although the time to achieve this symptom reduction ranged from one to five years. The delayed response trajectory showed improvements between two and five years while the episodic response trajectory showed gradual improvements between five and ten years. Thus, the achievement of sustained symptom remission is a process that can take several years and symptom course does not necessarily fixed after the first couple of years after diagnosis, as previously proposed (Birchwood et al., 1998). A study by Crumlish et al. (2009) also identified a subgroup of people with FEP that continued to improve between 4 and 8 years after diagnosis.

Similar studies examining positive symptom response within schizophrenia have found a comparable number of trajectories, usually characterized by amelioration of positive symptoms over time with the process taking up to 10 years (Levine et al., 2011). Furthermore, a small but significant group also showed a deteriorating course (Rabinowitz et al., 2007). While there appears to some convergence in results across studies, the OPUS cohort had fewer people that achieved sustained symptom remission and a greater variation in the trajectories displayed

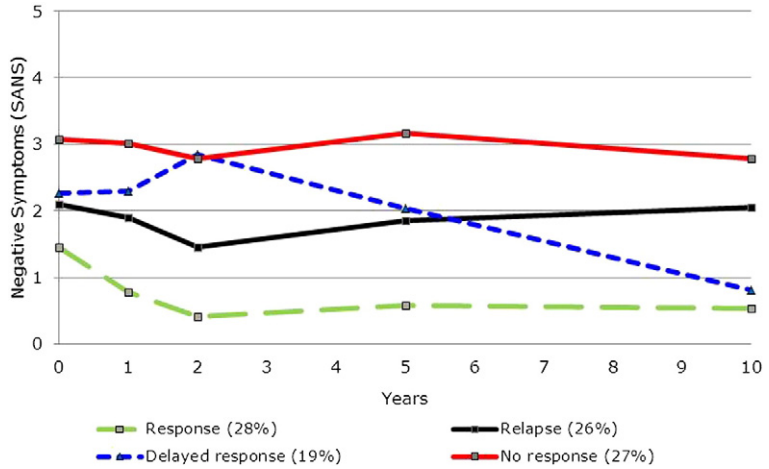

Fig. 2. Negative symptom trajectories over 10 year period (SANS scoring: 0 — absent, 1 — questionable, 2 — mild, 3 — moderate, 4 — marked, 5 — severe).

Table 2
Odds ratios from multivariable logistic regressions describing association between baseline characteristics and positive symptom trajectories.

Baseline Characteristics	Relapse (n = 75)		Delayed (n = 60)		Episodic (n = 64)		No response (n = 64)		Overall
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	p
Duration of untreated psychosis[a] (DUP)	**1.47 (1.21–1.80)**	**<0.001**	**1.27 (1.07–1.52)**	**0.01**	**1.32 (1.04–1.68)**	**0.02**	**1.34 (1.12–1.61)**	**0.002**	**<0.001**
Global functioning[b] (GAF-F)	0.99 (0.53–1.82)	0.96	1.23 (0.92–1.65)	0.17	0.62 (0.35–1.11)	0.11	**0.68 (0.47–0.99)**	**0.05**	**<0.001**
Substance abuse	**5.90 (1.81–19.2)**	**0.003**	2.33 (0.89–6.12)	0.09	1.64 (0.45–6.00)	0.46	**3.47 (1.39–8.65)**	**0.01**	**<0.001**
Standard treatment	0.92 (0.41–2.07)	0.85	1.39 (0.67–3.16)	0.44	0.50 (0.17–1.44)	0.20	0.95 (0.49–1.86)	0.89	0.47
Schizophrenia diagnosis	2.24 (0.69–7.27)	0.18	**7.09 (1.34–37.5)**	**0.02**	1.9 (0.60–6.04)	0.28	2.20 (0.67–7.21)	0.194	**<0.001**

Response trajectory is reference group (n = 233). Values in bold are statistically significant. OR: odds ratio. 95% CI — 95% confidence intervals.
[a] OR reflects a one year increase in DUP.
[b] OR reflects a 10 point increase in functioning on a 0–100 point GAF scale.

compared to the previous studies. It is possible, that previous studies that used number of days hospitalized as a proxy for symptoms lack the sensitivity to detect changes and thus may have oversimplified outcomes compared to studies based on clinical ratings, although further research is required.

Results from the multivariable regression analysis for baseline characteristics showed that longer duration of untreated psychosis, was associated with an increased risk of displaying a worse positive symptom prognosis for all four trajectories (relapse, delayed, episodic and no response) while substance abuse diagnosis was associated with an increased risk of displaying a relapsing and no response trajectory. Longer DUP has consistently been associated with poorer outcomes for positive symptoms (Harris et al., 2005; Jeppesen et al., 2008; Crumlish et al., 2009) and results from this study support this growing evidence base.

4.2. Negative symptom trajectories

Results from the LCA analysis identified four distinct trajectories for negative symptoms, where half the cohort failed to show a reduction over the ten years. People with sustained or persistent negative symptoms may experience significantly poorer functioning, worse psychological outcomes and lower rates of recovery compared to people who display reductions in negative symptoms over time (Strauss et al., 2010; Galderisi et al., 2012). Nearly a fifth of the cohort displayed significant reductions in their negative symptoms between two to ten years after their diagnosis, supporting the concept that change is possible several years after diagnosis. Finally, while over a quarter of the cohort displayed a response trajectory, the majority of these participants only displayed mild levels of negative psychopathology at baseline and therefore the relative amount of change shown over the 10 years was small.

The results from this study are in line with the current body of research on negative symptoms. Firstly, a number of studies have shown that people who experience negative symptoms often display a relatively stable course (Ginsberg et al., 2005) and often are relatively non-responsive to treatment (Erhart et al., 2006; Alphs, 2006). Secondly, numerous studies have indicated that greater levels of negative symptoms often predict poorer long term functioning and lower rates of recovery (White et al., 2009; Henry et al., 2010b; Milev et al., 2005; Alvarez-Jimenez et al., 2011; Rabinowitz et al., 2012; Strauss et al., 2012; Lambert et al., 2010; Alvarez-Jimenez et al., 2012).

A range of baseline factors were associated with worse negative symptom trajectories, with poor social functioning at baseline one of the most significant predictors. Social functioning prior and at illness onset could be an important marker for long-term prognosis for negative symptoms. Several studies have also shown that negative symptoms predict difficulties in functioning socially within schizophrenia (Buchanan, 2007; Pratt et al., 2005; Rocca et al., 2009). Other factors associated with poor negative symptom trajectories were having a schizophrenia diagnosis, higher disorganized symptoms at baseline and receiving standard treatment within the first two years of diagnosis.

While the findings for longer DUP and greater negative symptoms were non-significant in the multivariable model, DUP was a significant predictor in the univariable model. Thus, these results should be viewed with a degree of caution, given that numerous studies have previously found a significant association between the two factors (Verdoux et al., 2001; Norman et al., 2001; Boonstra et al., 2012; Perkins et al., 2005).

People receiving standard treatment were more six times more likely to display a delayed negative symptom trajectory compared to those people receiving assertive treatment. While this is an interesting result it should be remembered that this study was not designed to examine the differences between assertive and standard treatment and any conclusions from this finding must be very tentative. A number of promising studies have shown that psychosocial interventions such as cognitive behavioral therapy and cognitive remediation may be beneficial in alleviating negative symptoms (Klingberg et al., 2011; Rector and Beck, 2012; Elis et al., 2013) although more research is required.

The focus on symptom trajectories is important since the reduction of psychopathology is often has linked to improved functioning and ultimately clinical recovery (Silverstein and Bellack, 2008). It is also

Table 3
Odds ratios from multivariable logistic regressions describing association between baseline characteristics and negative symptom trajectories.

Baseline characteristic	Relapse (n = 129)		Delayed (n = 94)		No response (n = 134)		Overall
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	p
Disorganized symptoms[a]	**2.01 (1.09–3.71)**	**0.03**	1.44 (0.76–2.40)	0.27	**2.38 (1.38–4.22)**	**0.01**	**0.002**
Global functioning[b] (GAF-F)	0.79 (0.55–1.12)	0.86	0.86 (0.52–1.43)	0.56	**0.52 (0.35–0.78)**	**0.002**	**0.001**
Standard treatment	1.10 (0.43–2.87)	0.84	**6.03 (1.91–19.01)**	**0.01**	1.85 (0.79–4.34)	0.155	**0.002**
Sex (male)	1.94 (0.83–4.52)	0.13	1.31 (0.47–2.74)	0.79	**3.43 (1.45–8.13)**	**0.001**	**0.04**
Schizophrenia diagnosis	**5.70 (1.65–19.72)**	**0.01**	3.32 (0.86–12.84)	0.08	**8.86 (2.75–28.53)**	**<0.001**	**<0.001**
Inadequate social contact[c]	**3.13 (1.25–7.69)**	**0.02**	**3.44 (1.29–9.09)**	**0.01**	**5.55 (2.22–12.50)**	**<0.001**	**<0.001**
Pre-morbid social function[d] (PAS-S)	**1.34 (1.08–1.67)**	**0.01**	0.99 (0.77–1.28)	0.95	**1.38 (1.13–1.69)**	**0.002**	**0.002**

Response trajectory is reference group (n = 139). Values in bold are statistically significant. OR — odds ratio. 95% CI — 95% confidence intervals.
[a] OR reflects a 1 point increase in disorganized symptoms on a 1–5 point SAPS scale.
[b] OR reflects a 10 point increase in functioning on a 0–100 point GAF scale.
[c] Inadequate social contact — less than one contact a week with family or friend.
[d] OR reflects a 0.1 point decrease in pre-morbid social functioning on PAS with a scale range of 0.0–1.0.

important to acknowledge that recovery from mental illness is conceptualized as more than just the amelioration of symptoms but it also involves important subjective changes in which the person creates a meaningful identity and existence beyond having a mental illness often called personal or psychological recovery (Anthony, 1993). Several studies have shown that factors such as insight, self-esteem, levels of loneliness and beliefs about recovery can play a significant role in helping a person to recover psychologically from a serious mental illness (Neil et al., 2009; Morrison et al., 2013; Roe et al., 2011; Cavelti et al., 2012). Many clinicians and researchers advocate a holistic approach to recovery that encompasses both clinical and psychological aspects of the disorder.

5. Study limitations

As this study utilized a cohort from a randomized clinical trial, it is reasonable to assume that the two interventions impacted differentially on symptom trajectories within the first two years. The differences on primary outcomes (symptoms and functioning) between the two interventions had disappeared at 5 year follow-up. Results from the predictor analysis where treatment type was entered as a covariate, indicated that treatment type did not have a significant impact on any of positive symptom trajectories, and impacted on only one of the negative symptom trajectories, with those people receiving standard treatment more likely to display a delayed negative symptom trajectory compared to those receiving assertive treatment. The pragmatic decision to combine the two treatment groups into a single cohort provided a larger sample to perform a more robust statistical analysis with the caveat that the trajectories identified within the first two years are a oversimplification of the symptom course. A second limitation was that there were only 4 follow-up assessments conducted over a period of 10 years and these were not equally spaced over this period. Thus, the results are an oversimplification of the symptom trajectories manifested over this time. This is particularly evident for the trajectories identified between 5 and 10 years that are based on only two assessments and therefore may fail to capture the full variation in symptoms across this period. Despite this limitation, this study is still seen as having merit, given that there are very few studies that have followed a cohort of patients over such a long period of time and examined outcomes based on clinical assessments.

Thirdly, as with most longitudinal studies, there was incomplete follow-up information on symptom variables across the 10 year period. Therefore, we cannot rule out the possibility of a degree of bias in the estimated trajectories. However, the statistical method chosen (LCA analysis) is robust in the light of missing data and results will only be biased if the risk of a missing value depends on variables not included in the model (Little and Rubin, 1987). Since there was complete baseline information, the analysis will be unbiased as long as the risk of future values being missing depends only on the baseline level or the included covariates.

A fourth limitation is that there is no information regarding adherence to treatment after the initial two-year period. While all participants received standard treatment from years 2 to 10, it is not possible to explore how people in the cohort utilized this treatment or determine how treatment adherence may have impacted on symptom trajectories.

6. Clinical implications

The identification of different symptom trajectories and significant changes in symptom levels several years after diagnosis has important implications for the timing and length of interventions within first episode psychosis populations. People characterized with poor symptom trajectories could be targeted to receive extended intensive treatment or the provision of interventions at different times throughout the course of illness. These strategies could potentially improve long term outcomes. Furthermore, the identification of malleable factors that may impact on symptom trajectories such as DUP, substance abuse and social functioning could be targeted in future interventions, in order to promote a good prognosis. Currently, there is a lack of evidenced based interventions for negative symptoms and further research is needed to identify treatments that can impact on negative symptoms. The reduction of duration of untreated psychosis (Melle et al., 2008), cognitive behavioral therapy (Wykes et al., 2008) and cognitive remediation (Pfammatter et al., 2006) are promising psychosocial interventions that have been shown to potentially reduce negative symptoms, although more trials are required. Negative symptoms are recognized as a key factor in long-term functioning and the attainment of recovery (Austin et al., 2013; Milev et al., 2005; Henry et al., 2010a).

7. Conclusion

This study identified distinct trajectories for both positive and negative symptoms, supporting a heterogeneous illness course. Further studies using structured clinical assessments over longer time periods are required to establish an evidence base regarding the trajectories for positive and negative psychopathology and to identify the factors that influence these trajectories. This knowledge could be used to inform future interventions that potentially could impact on illness course and improve long-term outcomes within first episode psychosis.

8. Clinical points

- Trajectories for positive and negative symptoms are heterogeneous among people with first episode psychosis.
- Positive symptoms showed a general pattern of reduction and stabilization while negative symptoms show less change over a 10 year period.
- Significant changes in symptoms can occur many years after diagnosis and have implications for the prognosis and timing of interventions within first episode psychosis.

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Contributors

MN, OM and SFA conceived the study. MN rose the funding. SFA drafted the first manuscript. EBJ conducted the analysis and EBJ, MN, SFA, and CRH were involved in the interpretation of results. All authors critically revised the manuscript and approved the version submitted for publication.

Conflict of interest

All authors declare they have no conflict of interest.

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