Early-Stage Negative Symptom Trajectories and Relationships With 13-Year Outcomes in First-Episode Nonaffective Psychosis

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Negative symptoms are a key treatment target in early psychosis intervention. There is a paucity of research examining longitudinal course of negative symptoms across the initial years of treatment for first-episode psychosis using individual-based trajectory analysis. No study has been conducted investigating differential relationships of early-stage negative symptom trajectories with long-term distal outcomes. This study examined patterns and baseline predictors of negative symptom trajectories over the first 3 years of treatment in 138 patients aged 18–55 years presenting with first-episode nonaffective psychosis, using latent class growth analysis based on symptom ratings measured at 4 different time points (baseline, 1, 2, and 3 years). We further explored prospective relationships of identified trajectory classes with functional and negative symptom outcomes at 13-year follow-up. Our results revealed 3 distinct negative symptom trajectories including minimal-stable (59.6%), mild-stable (29.4%), and high-increasing (11.0%) trajectories. Poorer premorbid adjustment, more severe global cognitive impairment, and depressive symptoms at baseline were found to predict high-increasing trajectory. Among 3 trajectory classes, patients in high-increasing trajectory had the worst functional and negative symptom outcomes at 13-year follow-up, with post hoc analyses demonstrating significant outcome differences between high-increasing and minimal-stable trajectories. Our findings thus affirm a heterogeneous course of negative symptoms in first-episode psychosis and indicate that early-stage negative symptom trajectories are critically associated with long-term outcomes. Patients displaying persistently high negative symptom levels in the initial 3 years of treatment may represent a specific subgroup who necessitates an extended period of early intervention specifically targeting at negative symptoms to promote early functional recovery.

Key words: longitudinal course/first-episode psychosis/latent class growth analysis/prospective follow-up/functional outcome

Introduction

Negative symptoms have long been conceptualized as a core feature of psychotic disorders.^{1,2} Evidence has consistently indicated that negative symptoms are associated with pronounced functional impairment³ and limited response to available treatments,⁴ and constitute an unmet therapeutic need. Earlier research suggested progressive accrual and high stability of negative symptoms along the course of illness.^{5–7} More recent data, however, have revealed that negative symptoms are prevalent in people with first-episode psychosis (FEP)^{8,9} and may display substantial variability over time,¹⁰ particularly in the initial few years after illness onset.^{9,11} Furthermore, negative symptoms emerged in the early illness stage were found to strongly predict negative symptom severity and functional outcome at follow-up.^{12–14} As a significant proportion of FEP patients exhibit persistent functional disability even in the presence of positive symptom remission,^{13,15} negative symptoms thus represent a critical therapeutic target for promoting early functional recovery in first-episode populations.

In fact, better understanding of the longitudinal course patterns of negative symptoms following FEP is crucial to early intervention for psychosis. This facilitates early identification of a subgroup of patients at heightened risk for developing enduring negative symptoms and prompt delivery of targeted treatment for symptom alleviation and hence prevention of functional deterioration. However, owing to the heterogeneous course of negative symptoms in early psychosis, conventional approaches of

either examining temporal changes of negative symptoms by group averages or dichotomizing patients into those with vs without persistent negative symptoms (PNS)¹⁶ based on a priori operational criteria as adopted by most previous FEP research may mask the complexity of individual variation in symptom trajectory. Varying definitions applied for PNS status ascertainment including differences in duration (ranged from 6 to 12 months) and symptom exclusion criteria might also compromise cross-study comparability.^{17–23} It should also be noted that negative symptoms can be classified as primary vs secondary in nature, with the former being regarded as an “idiopathic form” of negative symptoms and the latter originated from confounding conditions including depression, paranoid suspiciousness, and drug-induced motor symptoms.²⁴ It is suggested that investigating primary negative symptoms, which represent a clinically more homogeneous construct, may facilitate unraveling the pathophysiology of and developing effective treatments for negative symptoms. Nonetheless, it is acknowledged that it may be difficult to reliably distinguish primary and secondary negative symptoms, particularly in early psychosis.²⁵

To address these limitations, recently, an individual-based longitudinal modeling including latent class growth analysis (LCGA) has been increasingly applied in mental health research. LCGA is a model-based, data-driven statistical approach that allows for probabilistic classification of participants into discrete subgroups based on their longitudinal trajectories.²⁶ Despite its methodological advantages, very few studies have been conducted to examine negative symptom course in FEP using individual-based trajectory analysis. Until now, there are only 4 published reports on FEP samples in this respect.^{27–30} Of note, 2 of these 4 studies examined negative symptom trajectories over a period of 1 year or less (ie, 6 weeks and 12 months).^{27,29} Given high variability in symptom levels during the first few years of treatment, such a short follow-up duration is unlikely to capture adequately the patterns of negative symptom course across the early phase of illness. In addition, 2 studies were clinical trial in design^{27,28} with patients being randomized to different treatment arms, which may differentially impact on negative symptom course, thereby introducing bias in study results. Furthermore, previous research examining baseline predictors for negative symptom trajectories in first-episode samples focused only on demographic and clinical variables. The potential effect of baseline cognitive functions on discriminating between negative symptom trajectories has not been explored. To the best of our knowledge, thus far, there is no published study investigating prospective relationships of early-stage negative symptom trajectories with distal illness outcomes in patients with FEP.

In this article, we report a prospective 13-year follow-up study in a cohort of Chinese patients presenting with first-episode nonaffective psychosis in Hong Kong

with an aim to: (1) identify distinct trajectories of negative symptoms over the first 3 years of treatment for an initial psychotic episode using LCGA; (2) to investigate baseline premorbid, clinical, and cognitive predictors discriminating between trajectory membership; and (3) to examine whether identified early-stage negative symptom trajectories were differentially associated with functional and negative symptom outcomes at 13-year follow-up.

Methods

Participants

Participants were recruited from outpatient and inpatient public psychiatric units that provided service for a catchment area in Hong Kong with a population of approximately 1.3 million. A total of 138 Chinese patients aged 18–55 years who were consecutively diagnosed as first-episode schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or brief psychotic disorder according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*³¹ were enrolled in a prospective 3-year follow-up study between 1997 and 2000.^{32,33} Patients who had substance-induced psychosis, alcohol or substance dependence, neurological disorder, learning disability, or had received antipsychotic treatment for more than 1 week prior to study entry were excluded.

All participants received initial assessment upon study intake. Subsequently, they were assessed after clinical stabilization with treatment (on average 42.6 days after study intake) and then re-evaluated at 1-, 2-, and 3-year follow-up. Participants were traced and reassessed with face-to-face interview 13 years after study enrolment. Tracing strategy followed a standardized protocol. Participants of the first-episode study cohort who were attending their regular psychiatric consultations were invited for reassessment in this 13-year follow-up study during their visits to the clinic. Participants who no longer received public psychiatric care were invited via telephone contact for reassessment. Targeted patients were considered lost-to-follow-up if multiple tracing attempts were unsuccessful. Findings regarding the relationship between duration of untreated psychosis (DUP) and symptom remission at 13-year follow-up have been reported elsewhere.³⁴ The study was approved by local institutional review boards and written informed consent was obtained from all participants.

Assessments

Diagnostic Assignment and Evaluation on Premorbid Adjustment and Onset Characteristics. Diagnostic ascertainment was based on longitudinal approach taking into consideration that diagnostic change may take place over time.³⁵ The final 13-year diagnosis of each participant was determined according to *DSM-IV* criteria using

all available information encompassing the entire follow-up period including the Chinese-bilingual Structured Clinical Interview for *DSM-IV* (Axis I, Patient version) (CB-SCID-I/P)³⁶ administered at baseline, at 3, and 13 years; informant histories; and medical records. Independent diagnostic assessments on a subset of sample ($n = 38$) demonstrated satisfactory concordance rate of 86%. Premorbid functioning was measured with the Premorbid Adjustment Scale (PAS)³⁷ based on information obtained via interviews with patients and relatives. We only included childhood (≤ 11 years) and early adolescence (12–15 years) periods for assessment to avoid any possible confounding with early symptoms because the onset of prodrome and psychosis usually occurs in late adolescence and early adulthood.³³ The PAS overall score was calculated by summing the scores on all items covering both periods and dividing by the total possible score (score range 0–1, higher score indicates lower functioning). The Interview for Retrospective Assessment of the Onset of Schizophrenia³⁸ was administered to determine DUP, age, and mode of onset of psychosis. DUP was defined as the time interval between the onset of positive symptoms and treatment initiation.

Symptom and Cognitive Assessments

Psychopathological assessment was conducted at initial presentation, at clinical stabilization, and then at 1-, 2-, and 3-year follow-up. Positive symptoms were measured using Positive and Negative Syndrome Scale (PANSS)³⁹ with intraclass correlation coefficient (ICC) being 0.83 for positive symptoms subscale. High Royds Evaluation of Negativity Scale (HEN)⁴⁰ was used to measure negative symptoms. It comprises 6 subscales and 18 items, which are rated along an anchored 5-point severity scale (range 0–4, higher score indicates more severe negative symptoms). Validation of HEN for use in Chinese patients with schizophrenia has previously been reported.⁴¹ ICCs for the subscales ranged from 0.74 (Thought) to 0.85 (Speech). In this study, we only included 4 of the 6 subscales, ie, Affect, Behavior, Speech, and Functioning subscales, for analysis as the remaining two, namely Thought and Appearance subscales, are more related to disorganization dimension.¹⁹ Montgomery–Asberg Depression Rating Scale (MADRS)⁴² was used to assess depressive symptoms. Cognitive assessment was conducted at clinical stabilization so as to reduce the state effects of acute psychosis on test performance of the patients. A brief standardized battery of cognitive tests comprising logical memory subtest (Wechsler Memory Scale—Revised, WMS-R-HK),⁴³ visual reproduction subtest (WMS-R-HK),⁴³ digit span (Wechsler Adult Intelligence Scale, WAIS-R-HK),⁴⁴ category verbal fluency, and Modified Wisconsin Card Sorting Test (MWCST) was administered.⁴⁵ A group of healthy controls ($n = 114$), matched with age, sex, and educational level, were recruited via advertisements and

were evaluated with the same battery of cognitive assessments as patients. Standardized z score for each of the cognitive tests was computed based on performance of healthy controls. Cognitive composite score for each patient was then calculated as a measure of global cognitive function for subsequent analysis by averaging the z scores of individual cognitive tests.

Assessments at 13-Year Follow-up

We focused our investigation of distal outcomes at 13-year follow-up on negative symptoms and functioning. Negative symptoms were measured by both PANSS negative symptom subscale and Scale for the Assessment of Negative Symptoms (SANS).⁴⁶ Global Assessment of Functioning (GAF) scale³¹ was used to measure overall functional levels of the patients. Psychosocial functioning was also measured using Role Functioning Scale (RFS)⁴⁷ that comprised 4 subscales, assessing functional levels of various domains including independent living and self-care, work productivity, and immediate and extended social networks. Psychopathological and functional outcome assessments at 13 years were conducted by a researcher (T.J.Y.M.) who was blind to baseline and 3-year outcome data of individual participants.

Statistical Analysis

LCGA was used to identify distinct negative symptom trajectories over the initial 3-year follow-up in first-episode cohort. LCGA is a person-centered statistical approach used to delineate homogenous subgroups (latent classes) of individuals with similar patterns of change over time.²⁶ In the current analysis, individual class membership was assigned on the basis of HEN total scores measured at 4 time points over 3 years, namely at clinical stabilization (as baseline assessment), 1, 2, and 3 years of follow-up, using full-information maximum likelihood estimation to account for missing data with the assumption that data were missing at random.⁴⁸ We opted for using symptom data collected at clinical stabilization rather than at initial presentation as baseline so as to minimize potential confounding effects of acute psychosis on measurement of negative symptom severity (see [Supplementary material](#) for additional sensitivity analysis of LCGA with initial presentation as baseline; [supplementary table S5](#) and [supplementary figure S3](#)). To determine the optimal number of trajectory classes, models with increasing number of latent classes (from 1- to 5-class models) were fitted to the data and the best-fitting model was selected according to the following goodness-of-fit indices: Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size-adjusted BIC (aBIC), Bootstrap Likelihood Ratio Test (BLRT), Lo–Mendell–Rubin Likelihood Ratio Test (LMR-LRT), and entropy. Lower values of AIC, BIC, and aBIC suggest a more parsimonious model,

whereas a significant BLRT and LMR-LRT (based on P value) indicate that this model (eg, a K class model) has a better fit than a model with one fewer latent classes (ie, a $K-1$ class model). Higher entropy also indicates better model fit. Aside from fit statistics, interpretability was also taken into consideration in model selection. LCGA was performed on Mplus, version 7.⁴⁹

To identify baseline predictors of trajectory membership, the estimated latent classes derived from LCGA were imported to SPSS, version 24⁵⁰ for a 2-step analysis. Candidate predictor variables including demographics, premorbid adjustment, and clinical and cognitive variables measured at clinical stabilization were compared between trajectory classes using ANOVAs and chi-square tests, as appropriate. Those variables that were found to be statistically significant in preceding analyses were then entered into a multinomial regression model to determine which candidate factors independently predicted trajectory membership. To examine whether early-stage negative symptom trajectories differentially related to functional and negative symptom outcomes at 13-year follow-up, a series of ANCOVAs were conducted, with previously identified baseline predictive variables of trajectory membership and baseline antipsychotic dose (using chlorpromazine equivalents)⁵¹ as covariates. Post hoc comparison analyses with Bonferroni correction for multiple comparisons were performed to further clarify the presence of significant differences between trajectory classes in various follow-up outcomes. DUP was log-transformed due to its skewed distribution. The level of statistical significance for all analyses was set at $P < .05$.

Results

Characteristics of the Sample

Of the 138 patients, 2 who did not complete assessment at clinical stabilization (baseline) were excluded from the analyses. Demographics, premorbid adjustment, and baseline clinical and cognitive profiles of 136 participants

are summarized in [supplementary table S1](#). Briefly, 136 participants were predominantly single (76.5%) and 44.1% were male. The mean age of the sample at intake was 31.6 years ($SD = 9.0$). The median DUP of the sample was 180 days (mean = 587.8 days, $SD = 969.8$). A flow of patients through the study is shown in [supplementary figure S1](#). A total of 119, 105, and 89 patients received 1-, 2-, and 3-year follow-up assessment, respectively. At 13-year follow-up, 88 participants (64.7%) were reinterviewed. Among those who did not complete 13-year follow-up evaluation, 13 were deceased (4 by suicide, 3 by suspected suicide, 3 by natural causes, and 3 with unknown causes), 5 refused reassessment, and 30 were lost to follow-up. Attrition analysis revealed no significant differences between completers and noncompleters in demographics, premorbid adjustment, or baseline clinical, cognitive, and treatment characteristics ([supplementary table S2](#)).

Latent Classes of Negative Symptom Trajectories

[Table 1](#) presents fit statistics for all the tested LCGA models. Overall, a 3-class solution was selected as the most parsimonious model. The 3-class solution outperformed the other models in terms of fit indices, yielding the lowest values in AIC and BIC (ie, the best model fit) and significant BLRT and LMR-LRT (indicating better fit than 2-class solution, with 4-class solution showing nonsignificant BLRT and LMR-LRT). Entropy of 3-class solution (0.84) was slightly lower than that of 2-class solution (0.87) but was much higher than all other models (0.71–0.72). The average class probabilities for the 3-class model were high (0.83–0.97), indicating high likelihood of correctly assigning patients to their respective latent class. Little's⁵² missing completely at random (MCAR) test was performed to verify whether the missing data of HEN ratings in the first 3 years of follow-up were missing at random or nonignorable (P value $< .05$ is interpreted as missing data being not MCAR). Our

Table 1. Goodness-of-fit Statistics of LCGA Models With 1–5 Class Solutions of Negative Symptom Trajectories

Number of Classes	Fit Statistics					
	AIC ^a	BIC ^a	aBIC ^a	Entropy ^b	BLRT (P) ^c	LMR-LRT (P) ^c
1	3414.18	3431.65	3412.67	—	—	—
2	3198.67	3224.88	3196.41	0.87	<.001	<.001
3	3155.05	3190.00	3152.04	0.84	<.001	<.009
4	3155.45	3199.14	3151.69	0.71	.429	.571
5	3155.79	3208.01	3151.06	0.72	.238	.181

Note: AIC, Akaike Information Criterion; aBIC, sample size–adjusted Bayesian Information Criterion; BIC, Bayesian Information Criterion; BLRT, Bootstrap Likelihood Ratio test; LCGA, Latent class growth analysis; LMR-LRT, Lo–Mendell–Rubin Likelihood Ratio test.

^aLower values (AIC, BIC, and aBIC) indicate better model fit.

^bHigher entropy indicates better model fit.

^cA significant BLRT or LMR-LRT (ie, $P < .05$) indicates that this model has a better fit than a model with one fewer class.

result of $P = .929$ ($\chi^2 = 142.2$) indicates that the missing data in the whole model were missing at random and the assumption of LCGA was fulfilled.

Negative symptom trajectories identified in the 3-class solution are illustrated in [figure 1](#). The first class was referred to as minimal-stable trajectory (59.6%, $n = 81$), which was characterized by consistently low to minimal levels of negative symptoms throughout 3-year follow-up. The second class was termed as mild-stable trajectory (29.4%, $n = 40$) in which patients displayed a pattern of mild negative symptoms with slight fluctuations over 3 years. The third class was referred to as high-increasing trajectory (11.0%, $n = 15$) in which patients exhibited high levels of negative symptoms at baseline with gradual symptom exacerbation across 3-year follow-up.

Predictors of Negative Symptom Trajectories

The 3 classes were compared on demographics, premorbid adjustment, and baseline clinical, cognitive, and treatment variables. As shown in [table 2](#), group differences were found in gender, educational levels, PAS overall score, cognitive composite score, MADRS total score, and negative symptom scores as expected (HEN total score and PANSS negative symptom subscale score). Multinomial regression analysis (using high-increasing trajectory as a reference category) revealed that patients in high-increasing class had significantly poorer premorbid adjustment, more severe baseline depressive symptoms, and poorer global cognitive functioning relative to those in minimal-stable class ([supplementary table S3](#)). No baseline variable was, however, identified by regression analysis to significantly differentiate between patients in high-increasing and mild-stable classes.

Relationships Between Trajectory Classes and 13-Year Outcomes

A series of ANCOVAs demonstrated significant differences among 3 trajectory classes in 13-year outcomes on

negative symptoms (SANS total score and PANSS negative symptom subscale score) and functioning (GAF score, RFS total score, and RFS domain scores in work productivity, independent living, and immediate social network) ([table 3](#)). Post hoc analyses revealed that patients in high-increasing class had significantly higher PANSS negative symptom subscale and SANS total scores, and lower GAF score, RFS total score, as well as RFS work productivity, independent living, and immediate social network domain scores than those in minimal-stable class ([table 4](#)). There was no significant difference between patients in high-increasing and mild-stable classes or between those in mild-stable and minimal-stable classes in any of the 13-year outcome variables on negative symptoms and functioning ([table 4](#)).

Discussion

In the current analysis, we identified 3 distinct negative symptom trajectories over the first 3 years of treatment for patients presenting with first-episode nonaffective psychosis. Overall, our results indicate heterogeneity of negative symptom course in the early stage of psychotic illness. Intriguingly, these 3 trajectories were largely parallel, differing mainly in terms of symptom severity. The majority of our sample (59.6%, classified as minimal-stable trajectory) exhibited consistently minimal negative symptoms across 3 years, whereas 29.4% were categorized as displaying mild-stable trajectory with steadily low levels of negative symptoms over time. Nonetheless, approximately 1 of 10 FEP patients (11.0%, classified as high-increasing trajectory) experienced persistently high levels of negative symptoms with gradual exacerbation across 3-year follow-up. Of note, there are significant between-study differences in latent trajectory patterns and proportions of patients in trajectory classes. In particular, prevalence of FEP sample running a course of sustained high levels of negative symptoms varied widely, ranging between 5.4% and 27% among those studies^{28–30} with follow-up

Fig. 1. Negative symptom trajectories over 3-year follow-up derived from latent class growth analysis. HEN, High Royds Evaluation of Negativity Scale.

Table 2. Comparison of Demographics, Baseline Clinical, and Cognitive Variables Among Patients in 3 Negative Symptom Trajectories

Variables	Mean (SD)/n (%)			F/χ^2_{2a}	P
	Minimal-Stable ($n = 81$)	Mild-Stable ($n = 40$)	High-Increasing ($n = 15$)		
Demographics					
Age at entry	31.0 (8.0)	32.0 (9.6)	33.8 (12.2)	0.67	.511
Male gender	34 (42.0)	15 (37.5)	11 (73.3)	6.06	.048*
Years of education	11.2 (3.1)	9.3 (3.8)	10.1 (2.3)	4.59	.012*
Unemployed	46 (57.5)	13 (34.2)	6 (42.9)	5.85	.054
Single, marital status	61 (75.3)	30 (75.0)	13 (86.7)	0.98	.614
Illness and onset characteristics					
PAS overall score	0.2 (0.1)	0.3 (0.1)	0.3 (0.1)	4.27	.016*
Age at onset of psychosis	29.4 (7.8)	30.6 (10.4)	31.5 (11.3)	0.46	.635
Gradual onset (>4 wk)	41 (50.6)	18 (45.0)	3 (20.0)	4.791	.091
Log DUP ^b	2.1 (0.9)	2.1 (0.8)	2.6 (0.7)	2.16	.120
Schizophrenia spectrum disorder ^c	63 (77.8)	34 (85.0)	15 (100.0)	4.574	.102
Symptom severity					
PANSS positive symptom score	9.1 (2.4)	9.9 (3.4)	10.6 (3.4)	2.39	.096
PANSS negative symptom score	9.8 (3.0)	15.1 (6.2)	21.7 (6.8)	50.12	<.001***
HEN total score	6.2 (5.6)	17.7 (8.5)	24.9 (8.7)	67.53	<.001***
MADRS total score	2.0 (5.3)	6.0 (6.8)	5.3 (5.4)	6.89	.01*
Cognitive composite score ^d	-0.3 (0.6)	-0.8 (1.0)	-0.9 (1.0)	8.35	<.001***
Antipsychotic dosage ^e , mg	312.9 (445.1)	342.7 (401.3)	410.1 (399.9)	0.39	.681

Note: DUP, Duration of untreated psychosis; HEN, High Roysd Evaluation of Negativity Scale; MADRS, Montgomery–Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale.

^aANOVA and chi-square test were conducted for continuous and categorical variables, respectively.

^bDUP was log transformed due to its skewed distribution.

^cSchizophrenia spectrum disorder included schizophrenia, schizoaffective disorder, and schizophreniform disorder. Other nonaffective psychoses included brief psychotic disorder and delusional disorder.

^dCognitive composite score for each participant was calculated as a measure of global cognitive function by averaging the z scores of individual cognitive tests.

^eChlorpromazine equivalents were computed for analysis.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 3. 13-Year Functional and Negative Symptom Outcome Comparison Among Patients of 3 Negative Symptom Trajectories

Variables	Mean (SD)			F^a	P
	Minimal-Stable ($n = 56$)	Mild-Stable ($n = 24$)	High-Increasing ($n = 8$)		
Functional outcome					
GAF score	68.6 (16.1)	58.6 (16.3)	50.1 (13.1)	4.37	.016*
RFS total score	22.0 (3.8)	18.8 (4.2)	16.0 (4.1)	6.21	.003**
RFS work productivity	5.0 (1.7)	3.9 (1.8)	2.8 (2.0)	4.22	.019*
RFS independent living	6.5 (0.8)	5.8 (1.1)	5.0 (1.5)	5.36	.007**
RFS immediate social network	5.2 (1.1)	4.6 (1.1)	4.3 (0.7)	4.04	.022*
RFS extended social network	5.3 (1.2)	4.5 (1.0)	4.0 (1.2)	2.70	.074
Negative symptom outcome					
SANS total score	6.6 (6.6)	11.3 (11.2)	19.3 (10.3)	5.73	.005**
PANSS negative symptom score	9.0 (2.5)	11.0 (3.9)	13.5 (3.8)	3.96	.024*

Note: Abbreviations are explained in the footnote to “Table 2”. GAF, Global Assessment of Functioning Scale; MADRS, Montgomery–Asberg Depression Rating Scale; RFS, Role Functioning Scale; SANS, Scale for Assessment of Negative Symptoms.

^aANCOVA were performed with PAS overall score as well as baseline MADRS total score, cognitive composite score, and chlorpromazine equivalent dose as covariates. In addition, supplementary comparison analyses on PANSS positive symptom score ($F = 0.36$, $P = .696$) and MADRS total score ($F = 0.04$, $P = .962$) at 13-year follow-up were conducted but showed no statistical significance.

* $P < .05$, ** $P < .01$.

Table 4. Post Hoc Comparison Analyses on Functional and Negative Symptom Outcomes Between Patients With Different Negative Symptom Trajectories^a

Variables	High-Increasing vs Minimal-Stable			High-Increasing vs Mild-Stable			Mild-Stable vs Minimal-Stable		
	Mean difference	SE	P	Mean difference	SE	P	Mean difference	SE	P
Functional outcome									
GAF score	-18.48	6.88	.030*	-8.86	6.86	.610	-9.62	4.65	.130
RFS scores									
RFS total score	-5.38	1.67	.006**	-2.64	1.67	.354	-2.75	1.13	.052
Work productivity score	-2.07	0.76	.024*	-1.12	0.75	.423	-0.95	0.51	.205
Independent living score	-1.23	0.40	.010*	-0.63	0.40	.360	-0.59	0.27	.098
Immediate social network score	-1.13	0.45	.042*	-0.49	0.45	1.830	-0.64	0.30	.117
Negative symptom outcome									
SANS total score	11.85	3.53	.004**	7.97	3.54	.082	3.87	2.45	.354
PANSS negative symptom score	3.51	1.28	.023*	2.18	1.28	.278	1.33	0.88	.410

Note: Abbreviations are explained in the footnote to “Tables 2 and 3.”

^aPost hoc pairwise comparison analyses with Bonferroni correction were performed. Only outcome variables demonstrating significant between-group differences in analyses of covariance (table 3) were included in post hoc analyses.

* $P < .05$, ** $P < .01$.

duration of 1 year or above for trajectory analysis. These inconsistent findings may partly be attributable to methodological variations across studies, including follow-up duration and time intervals between assessments, use of different scales for negative symptom measurement, and naturalistic observational vs clinical trial design. Contrary to several prior reports^{27,29,30} that detected trajectories characterized by early significant symptom reduction, we failed to find such an “early-responder” course pattern in our study. One possible explanation is that our lack of interim assessment between baseline and 1-year follow-up precludes us from capturing short-term symptom changes across an initial year of treatment. Alternatively, our choice of adopting symptom assessment conducted after clinical stabilization of first psychotic episode as baseline time point for LCGA modeling, instead of upon initial presentation as most past studies did, might also contribute to such discrepant results by minimizing state effect of acute psychosis on our baseline negative symptom measurement. In fact, substantial evidence has demonstrated that negative symptom reduction correlates with positive symptom improvement and global treatment response.^{53,54} Thus, the trajectory denoting an apparent negative symptom improvement following commencement of antipsychotic treatment as observed by some previous studies might primarily be secondary to positive symptom resolution (Note: Post hoc analyses comparing positive symptom levels among trajectory classes revealed no significant differences at 1-, 2-, and 3-year follow-up, with all P values $> .05$).

Our study revealed that premorbid adjustment, baseline global cognition, and depressive symptoms significantly differentiated patients in high-increasing

trajectory from those in minimal-stable trajectory. Our finding that poorer premorbid functioning predicted trajectory with persistently high levels of negative symptoms concurs with that of some previous investigations^{28,29} using similar latent growth modeling approach to evaluate longitudinal patterns of negative symptoms in FEP. This is also consistent with a large body of evidence indicating poor premorbid adjustment as a robust predictor of more severe negative symptoms in first-episode samples.^{33,55} This study is the first to examine relationship between baseline cognitive function and negative symptom trajectories in FEP, and demonstrated that greater global cognitive impairment independently predicted a continuous course of severe negative symptoms across the initial years of treatment. Our result is thus in line with some, though not all, previous first-episode studies revealing that more severe baseline cognitive dysfunction was associated with PNS status.^{20,22,23} This also accords with findings of a recent meta-analytic review showing that patients with deficit syndrome,⁵⁶ ie, enduring primary negative symptoms sustained for at least 1 year, significantly underperformed than nondeficit counterparts in all cognitive domains.⁵⁷ Conversely, it was an unexpected finding that high-increasing trajectory was related to more severe baseline depression that is widely recognized as an important source of secondary negative symptoms.⁵⁸ Nonetheless, our post hoc analyses comparing depressive symptom levels among trajectory classes revealed no significant differences at 1-, 2-, and 3-year follow-up (all P values $> .05$), suggesting that between-trajectory differences in negative symptom levels were unlikely due to confounding effect of depression but indicate inherent course patterns of

negative symptoms. We also repeated LCGA and subsequent predictor analyses for trajectory membership in a subsample of FEP patients without clinically significant depressive symptoms at baseline in order to minimize potential confounding effect of severe depression on trajectory analysis. The additional analyses yielded 3 trajectory classes that were similar to those derived from the entire patient sample and identified the same baseline predictor variables (ie, including baseline depression) for negative symptom trajectories as our original analyses (see [Supplementary material](#) for additional analyses; [supplementary tables S5](#) and [S6](#), and [supplementary figure S3](#)). Alternatively, it is possible that depression assessed by MADRS might also partly reflect genuine negative symptom severity at baseline due to measurement bias. In fact, several items in MADRS including “lassitude” and “inability to feel” might overlap with experiential subdomain of negative symptoms (ie, anhedonia and avolition). This is an important limitation of the study and echoes the evidence suggesting that depression rating instrument that is designed specifically for schizophrenia should be used so as to accurately differentiate depressive symptoms from negative symptoms and other symptom dimensions.⁵⁹

To the best of our knowledge, this is the first study examining prospective relationships of early-stage negative symptom trajectories of FEP sample and distal illness outcomes. Our results indicate that, among 3 trajectory classes, patients with high-increasing trajectory had the worst outcomes in negative symptoms, global functioning, as well as several individual functional domains at 13-year follow-up, with post hoc comparisons further demonstrating significant outcome differences between high-increasing and minimal-stable trajectories. Our data hence provide evidence suggesting that early-stage negative symptom trajectory pattern is a valuable and potentially powerful prognostic indicator of long-term clinical and functional outcomes. This also affirms the critical role of negative symptoms as a key treatment target in early intervention for psychosis. However, given the small sample size with participant attrition at 13-year follow-up, these findings should be treated with caution and regarded as exploratory. This is particularly relevant to high-increasing trajectory vs mild-stable trajectory comparison analyses. Our findings of lack of outcome differences between these 2 trajectories might be due to the small sample size, which precluded us from identifying subtle yet potentially significant group differences. Replication with larger sample size is required to confirm our preliminary results of differential relationships between early-stage negative symptom trajectories and distal outcomes.

The study results have important clinical implications. Although the majority of FEP patients experienced minimal to mild negative symptoms in the first 3 years of follow-up, 11% were categorized as displaying

high-increasing trajectory of negative symptoms that predicted the worst symptom and functional outcomes 13 years after first presentation relative to those in other trajectory classes. Thus, patients with persistently high levels of negative symptoms over the initial years of treatment might represent a subgroup of first-episode populations who warrant an extended period of intensive early intervention targeting at negative symptom alleviation and functional enhancement. This in turn underscores the need for close monitoring of both severity and temporal stability of negative symptoms emerged in the initial stage of treatment to facilitate early detection of individuals at high risk for enduring severe negative symptoms, as well as development of effective treatments specific to negative symptoms. In fact, there is recent evidence, albeit mainly in chronic schizophrenia, suggesting that psychotherapeutic interventions including cognitive behavioral therapy and cognitive remediation are effective in improving negative symptoms.^{60,61} In particular, given that baseline cognitive impairment was found to predict high-increasing trajectory, further research is required to examine the efficacy of cognitive remediation on negative symptom reduction specifically in FEP patients.

Several methodological limitations warrant consideration in interpreting the study results. First, the relatively modest sample size of our cohort may preclude us from detecting potentially more subtle symptom trajectory patterns. Sample size reduction by participant attrition at 13-year follow-up further compromised our comparison analyses among 3 trajectories on distal outcomes. Second, the current analysis only focused on negative symptoms in the first 3 years of treatment as no interim assessments were conducted between 3 and 13 years of follow-up. Hence, longer-term symptom course could not be captured by the study. Third, we did not further delineate negative symptoms into primary vs secondary in nature. Thus, we could not rule out the possibility that our LCGA-derived trajectory patterns might still be influenced by the effects of secondary negative symptoms. Fourth, although HEN was specifically designed for negative symptom assessment, it may not well align with the 5 core domains of negative symptom construct recognized by NIMH-initiated Consensus Development Conference on Negative Symptoms in 2005.⁶² Application of next-generation negative symptom scales⁶³ developed according to the recommendations of consensus conference should be considered in future research to facilitate more comprehensive evaluation of negative symptoms for trajectory analysis in FEP populations.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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