20-year trajectories of positive and negative symptoms after the first psychotic episode in patients with schizophrenia spectrum disorder: results from the OPUS study

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This study aimed to identify the 20-year trajectories of positive and negative symptoms after the first psychotic episode in a sample of patients with an ICD-10 diagnosis of schizophrenia spectrum disorder, and to investigate the baseline characteristics and long-term outcomes associated with these trajectories. A total of 373 participants in the OPUS trial were included in the study. Symptoms were assessed at baseline and after 1, 2, 5, 10 and 20 years using the Scales for the Assessment of Positive and Negative Symptoms. We used latent class growth mixture modelling to identify trajectories, and multinominal regression analyses to investigate predictors of membership to identified trajectories. Five trajectories of positive symptoms were identified: early continuous remission (50.9% of the sample), stable improvement (18.0%), intermittent symptoms (10.2%), relapse with moderate symptoms (11.9%), and continuous severe symptoms (9.1%). Substance use disorder (odds ratio, OR: 2.83, 95% CI: 1.09-7.38, p=0.033), longer duration of untreated psychosis (OR: 1.02, 95% CI: 1.00-1.03, p=0.007) and higher level of negative symptoms (OR: 1.60, 95% CI: 1.07-2.39, p=0.021) were predictors of the relapse with moderate symptoms trajectory, while only longer duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, p=0.030) predicted membership to the continuous severe symptoms trajectory. Two trajectories of negative symptoms were identified: symptom remission (51.0%) and continuous symptoms (49.0%). Predictors of the continuous symptoms trajectory were male sex (OR: 3.03, 95% CI: 1.48-6.02, p=0.002) and longer duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, p=0.034). Trajectories displaying continuous positive and negative symptoms were linked to lower neurocognition, as measured by the Brief Assessment of Cognition in Schizophrenia (BACS) (z-score: –0.78, CI: –1.39 to –0.17, for continuous positive symptoms; z-score: –0.33, CI: –0.53 to –0.13, for continuous negative symptoms). The same trajectories were also linked to higher use of antipsychotic medication at 20-year follow-up (continuous positive symptoms: 78%; continuous negative symptoms: 67%). These findings suggest that the majority of patients with first-episode schizophrenia spectrum disorder have a trajectory with early stable remission of positive symptoms. Long duration of untreated psychosis and comorbid substance abuse are modifiable predictors of poor trajectories for positive symptoms in these patients. In about half of patients, negative symptoms do not improve over time. These symptoms, in addition to being associated with poor social and neurocognitive functioning, may prevent patients from seeking help.

Key words: First-episode psychosis, schizophrenia spectrum disorder, positive symptoms, negative symptoms, trajectories of symptoms, predictors of symptom trajectories, social functioning, neurocognition

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Schizophrenia affects roughly 1-2% of the world's population[1,2] and is a leading cause of disability worldwide[3]. The disorder often has its onset early in life and is associated with long-term impairments of social and occupational functioning[4], and with significant adversities to both patients and their relatives.

The evolution of the disorder can vary between patients[5]. Some are affected by chronic symptoms, while others experience phases of remission or full recovery[6-8]. The main clinical manifestations are positive and negative symptoms, but patients may also exhibit cognitive deficits and experience a wide range of other subjective symptoms[9,10]. This means that the large group of patients collectively diagnosed with a schizophrenia spectrum disorder experience different patterns of illness course, some much worse than others. Latent class models and growth mixture modeling enable today the identification of clusters of individuals with specific trajectories of symptoms[11], allowing to explore their sociodemographic, clinical and social functioning correlates.

Studies conducted in the 20st century reported great heterogeneity in the course of illness among first-episode psychosis patients[12,13]. Their cross-sectional design provided valuable knowledge on levels of psychopathology at specific timepoints, but no information on illness manifestation over time. Research collecting longitudinal data has contributed to a better understanding of the course of illness. The Suffolk County Study explored trajectories of social functioning, reporting that 75% of patients with psychotic disorders had severe and persistent social impairments[14]. Other studies have determined symptom trajectories in schizophrenia, with follow-ups ranging from weeks to a maximum of 10 years[10]. In these studies, most patients experienced early or delayed improvement of positive symptoms followed by stable symptom levels, while a large group of patients usually experienced only minimal improvement of negative symptoms[10,15]. These latter symptoms are of increasing interest, since patients with a persistence of these symptoms are at high risk of poor outcomes, such as social isolation, unemployment and poor health[16,17]. In addition, treatment options for persistent negative symptoms are scarce[18,19]. Poor symptom trajectories have been previously associated with some sociodemographic and clinical variables, such as male sex, poor premorbid functioning, substance abuse, and a schizophrenia diagnosis[20,21].

Determining symptom trajectories in a modern-day treatment environment and characterizing homogeneous subgroups of patients with schizophrenia spectrum disorder based on long-term symptom levels is a research and clinical priority, as it might help the planning of treatment and possibly the identification of bio-

logical correlates. Identifying characteristics that predict chronic illness could also help target new integrated interventions.

The aim of this study was to identify 20-year trajectories of positive and negative symptoms after the first psychotic episode in patients with an ICD-10 diagnosis of schizophrenia spectrum disorder. We also examined if any baseline characteristics could predict illness trajectories, and explored whether specific illness trajectories were associated with clinical and functional outcomes after 20 years.

METHODS

Study design and participants

This 20-year follow-up study reassessed participants from the OPUS randomized controlled trial. Five hundred seventy-eight participants with an incident schizophrenia spectrum diagnosis (ICD-10 classification: F20-F25, F28-F29) were recruited between 1998 and 2000. Inclusion criteria were a first psychotic episode, age between 18 and 45 years, and not having received more than 12 weeks of continuous antipsychotic treatment. Patients were randomized to specialized early intervention treatment (comprised of assertive community treatment, family involvement, and psychoeducation) or treatment as usual[22]. All participants were given a comprehensive description of the study and provided written consent.

Patients were assessed at baseline and after 1, 2, 5, 10 and 20 years. Each follow-up was conducted by independent clinical staff blinded to the original treatment allocation. Participants were assessed using semi-structured face-to-face interviews followed by questionnaires. Regular sessions were conducted to secure high inter-rater reliability in the use of the assessment instruments.

For this current study, we combined the two treatment groups into one large cohort, because our main aim was to explore heterogeneity in the development of positive and negative symptoms, and allocation to either specialized early intervention treatment or treatment as usual had been found not to affect clinical outcomes at 5 years[22]. In the 20-year trajectory analysis, we included 373 participants with complete data on symptoms at baseline and follow-up. Of these patients, 23 participated in two interviews, 31 in three interviews, 94 in four interviews, 132 in five interviews and 93 in all six interviews (see supplementary information).

Measures of positive and negative symptoms

Symptoms were assessed at baseline and after 1, 2, 5, 10 and 20 years using the Scale for the Assessment of Positive Symptoms (SAPS)[23] and the Scale for the Assessment of Negative Symptoms (SANS)[24]. For both dimensions, we calculated composite scores ranging from 0 to 5. The "positive dimension" was the mean score of the global ratings for hallucinations and delusions. The "negative dimension" was the mean score of all four global ratings of negative domains in the SANS[25]. We regarded a symptom score of 2 or less on all global ratings of symptoms as clinical remission[26].

Baseline risk factors

The variables examined as possible baseline predictors of trajectory membership were: age; sex; main ICD-10 diagnosis ascertained by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[27]; diagnosis of substance use disorder ascertained using the same interview; global level of functioning measured by the Global Assessment of Functioning (GAF) scale (from 0, poor to 100, good)[28]; negative, positive and disorganized symptoms assessed using the SANS and the SAPS and rated as a continuous variable from 0 to 5; allocation to either early intervention treatment or treatment as usual; completion or not of high school; premorbid social and academic functioning assessed using the Premorbid Adjustment Scale (PAS)[29]; duration of untreated psychosis assessed by the Interview for Retrospective Assessment of Onset of Schizophrenia (IRAOS)[30] and defined as the number of months with at least one psychotic symptom definitely present until the initiation of treatment[31].

Distal outcomes

We examined the association between trajectories of positive and negative symptoms and distal outcomes measured at the 20-year follow-up. The outcomes measured were: a) rate of recovery, defined as no psychotic episode, no psychiatric hospitalization and no use of supported housing in the past two years, being engaged in studying or working, and a present GAF score ≥60; b) for positive symptom trajectories, remission of negative symptoms; for negative symptom trajectories, remission of positive symptoms; c) social functioning assessed by the Personal and Social Performance (PSP) scale[32], which measures four domains of social functioning (useful activities, personal relationships, self-care, aggressive and disturbing behaviour), combined and rated with a score ranging from 0 to 100; d) cognitive functioning measured by the Brief Assessment of Cognition in Schizophrenia (BACS)[33] and reported as z-score; e) current diagnosis of schizophrenia based on the SCAN interview; and f) current treatment with antipsychotic medication.

Statistical analysis

We applied latent growth mixture modelling (LGMM) and latent class growth analysis (LCGA) to estimate trajectories of positive and negative symptom dimensions[34]. These are data-driven, person-centered approaches, that identify population subgroups (classes) based on prototypical patterns in intercepts and slopes. To handle missing data, we applied the full information maximum likelihood approach[35].

We estimated LGMM and LCGA models with different growth functions (i.e., linear, quadratic or cubic) and an increasing number of classes. We examined a number of model fit estimates and model features to select the model with the best fit of the data, including Akaike information criteria (AIC), Bayesian information

criteria (BIC) and sample-size adjusted BIC (adj. BIC), entropy of the model, class size and accuracy, and test of model fit with addition of an extra class by Lo-Mendell-Rubin and Vuong-Lo-Mendell-Rubin likelihood ratio tests.

We tested baseline variables as predictors of class membership by applying the Three-Step approach[36], in which covariates are not included in the modelling of trajectories but treated as auxiliary variables, so that they do not influence the formation of trajectories. Therefore, class membership is established first, and subsequently predictors for membership of identified trajectories are examined. We first tested baseline variables univariably, and then included all significant covariates in a multivariable multinomial logistic regression model. Level of significance was set at $p<0.05$. The results are presented as odds ratios (OR) with 95% confidence intervals (95% CI) and corresponding p values. In order to examine the association between trajectory membership and distal outcomes, we used the Lanza method[37]. All statistical analyses were conducted in Mplus statistical software version 7.

RESULTS

Dropout analysis

A total of 373 participants were included in this study. In the dropout analysis, we found that participants did not differ from non-participants with respect to baseline psychopathological characteristics (including the proportion of those with a diagnosis of schizophrenia and of substance use disorder, and the mean scores on the positive and negative dimensions), the median duration of untreated psychosis, the employment rate, the proportion of those who completed high school education, and the mean scores for premorbid social and academic functioning. Participants were slightly younger than non-participants (26.2±6.2 vs. 27.8±6.8 years), were less frequently male (55.1% vs. 64.0%), had higher levels of global functioning (mean GAF score: 41.0±13.7 vs. 37.7±11. 9), and had higher rates of independent living (95.5% vs. 87.6%) (see also supplementary information).

Trajectories of positive symptoms

For positive symptoms, we estimated a series of linear, quadratic and cubic term LCGA and LGMM models from one to six classes (see supplementary information). We chose the five-class model based on likelihood ratio tests indicating that it had a superior goodness of fit compared with the four-class model. Entropy scores were high for both the four- and five-class models (0.834 vs. 0.949), but the individual class accuracy scores in the five-class model were higher (all above 0.95), expressing a better classification accuracy (see supplementary information).

We named the five positive symptom trajectories as follows: *early continuous remission* (50.9% of the sample), characterized by early and continuous remission of symptoms; *stable improvement* (18.0%), marked by a slower decrease of symptoms in the first five years followed by stabilization; *intermittent symptoms* (10.2%), characterized by relapse and remission of symptoms; *relapse with moderate symptoms* (11.9%), marked by improvement of symptoms in the first years followed by a slow but continuous increase of symptoms subsequently; and *continuous severe symptoms* (9.1%), characterized by a small decrease in symptoms in the first year followed by a stable continuous course of symptoms (see Figure 1).

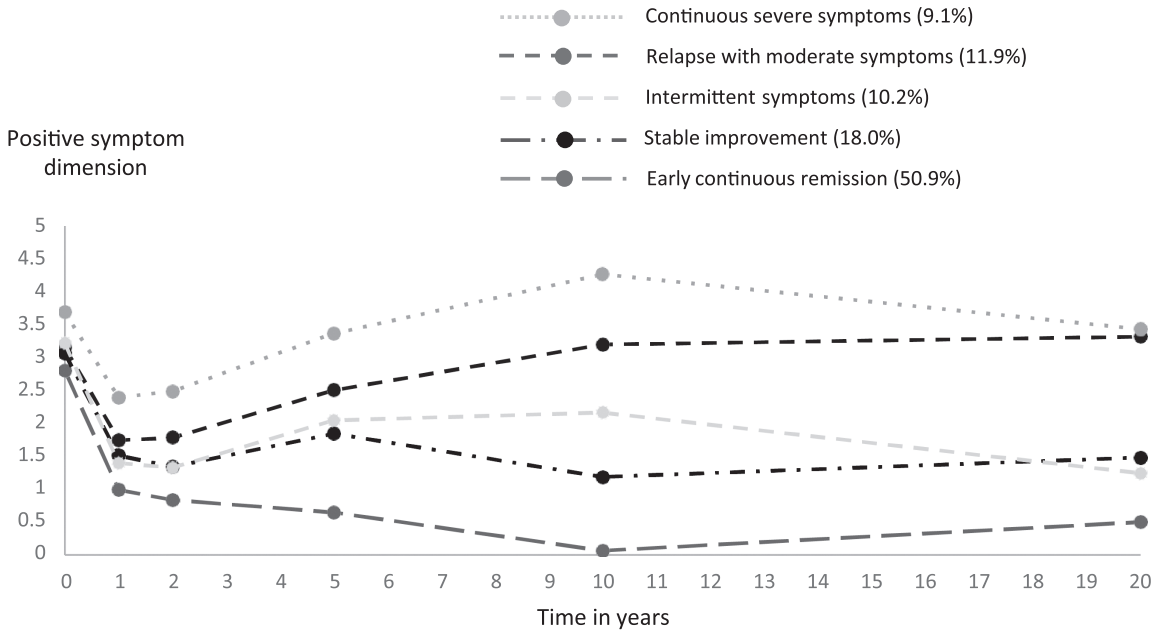

Figure 1 20-year trajectories of positive symptoms after the first psychotic episode in patients with an ICD-10 diagnosis of schizophrenia spectrum disorder

Trajectories of negative symptoms

For negative symptoms, we estimated a series of LCGA and LGMM models from one to five classes (see supplementary information). The two-class LCGA model was chosen because it had higher entropy and class accuracies (both classes above 0.93) than models with additional classes (all class accuracies lower than 0.93). The two trajectories of negative symptoms were named *symptom remission* (51.0% of the sample), characterized by a low mean level of negative symptoms initially, followed by remission within the first two years, and *continuous symptoms* (49.0%), marked by a high mean level of negative symptoms at baseline and no changes over time (see Figure 2).

Baseline predictors of trajectory membership

Positive dimension

Using univariable multinomial logistic regression analysis, we first identified baseline characteristics associated with positive symptom trajectories using *early continuous remission* as a reference (see supplementary information). Significant predictors were then entered into multivariable analysis. Substance use disorder (OR: 2.83, 95% CI: 1.09-7.38, p=0.033), longer duration of untreated psychosis (OR: 1.02, 95% CI: 1.00-1.03, p=0.007), and higher level of negative symptoms (OR: 1.60, 95% CI: 1.07-2.39, p=0.021) remained significant predictors of membership to the *relapse with moderate symptoms* trajectory, while only duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, p=0.030) predicted membership to the *continuous severe symptoms* trajectory. Male sex (OR: 3.69, 95% CI: 1.42-9.58, p=0.007) predicted membership to the trajectory of *intermittent symptoms* (see Table 1).

Negative dimension

A similar univariable multinomial logistic regression analysis was conducted for predictors of negative symptom trajectories (see supplementary information). In multivariable analysis, male sex (OR: 3.03, 95% CI: 1.48-6.02, p=0.002) and longer duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, p=0.034) increased the risk of belonging to the *continuous symptoms trajectory* compared with the *symptom remission* trajectory. Higher level of global functioning (OR: 0.95, 95% CI: 0.92-0.98, p=0.001) and finishing high school (OR: 0.41, 95% CI: 0.17-1.00, p=0.049) were associated with lower risk of belonging to the *continuous symptoms* trajectory (see Table 2).

Associations between trajectory membership and distal outcomes

Positive dimension

Social functioning scores at the 20-year follow-up were significantly higher in patients with the *early continuous remission* trajectory (mean PSP score: 60.7, CI: 57.6-63.8) and the *stable improvement* trajectory (mean PSP score: 59.0, CI: 52.7-65.3) compared to those with the other trajectories (mean PSP scores between 40.4 and 47.9). Patients with the *early continuous remission* trajectory had a significantly higher recovery rate (22%) than those with the other trajectories. Neurocognitive function was significantly more impaired in patients with the *continuous severe symptoms* trajectory (z-score: –0.78, CI: –1.39 to –0.17) than in those with the *early continuous remission*, *stable improvement* and *intermittent symptoms* trajectories (see Table 3).

The number of patients qualifying for a schizophrenia diagno-

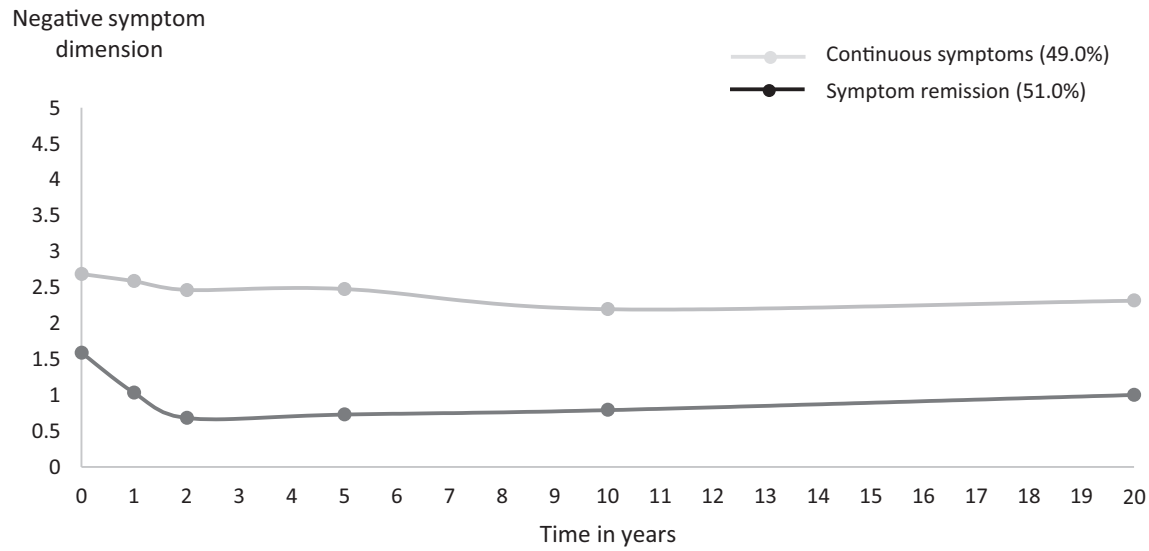

Figure 2 20-year trajectories of negative symptoms after the first psychotic episode in patients with an ICD-10 diagnosis of schizophrenia spectrum disorder

Table 1 Predictors of membership to positive symptom trajectories using patients with the *early continuous remission* trajectory as reference group

	Stable improvement		Intermittent symptoms		Relapse with moderate symptoms		Continuous severe symptoms	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Male	1.01 (0.49-2.08)	0.977	3.69 (1.42-9.58)	0.007	2.47 (0.96-6.38)	0.061	0.84 (0.35-2.03)	0.697
Completed high school	1.24 (0.58-2.67)	0.575	0.36 (0.10-1.25)	0.108	0.51 (0.14-1.83)	0.301	0.74 (0.24-2.29)	0.602
Employment	1.32 (0.66-2.66)	0.437	0.67 (0.22-2.02)	0.483	0.46 (0.13-1.73)	0.253	0.49 (0.14-1.69)	0.257
Substance use disorder	0.90 (0.37-2.16)	0.806	0.75 (0.25-2.28)	0.747	2.83 (1.09-7.38)	0.033	2.05 (0.78-5.40)	0.148
Poorer level of premorbid social functioning	2.50 (0.49-12.82)	0.270	2.36 (0.17-32.44)	0.521	2.47 (0.24-25.29)	0.445	0.88 (0.04-19.51)	0.934
Poorer level of premorbid academic functioning	5.85 (0.67-50.95)	0.081	0.16 (0.01-2.20)	0.172	2.30 (0.11-46.74)	0.588	2.55 (0.09-68.77)	0.577
Longer duration of untreated psychosis	1.01 (1.00-1.02)	0.179	1.01 (1.00-1.02)	0.122	1.02 (1.00-1.03)	0.007	1.01 (1.00-1.02)	0.030
Higher level of global functioning	0.99 (0.96-1.01)	0.349	0.97 (0.93-1.01)	0.168	1.00 (0.96-1.04)	0.985	0.99 (0.95-1.02)	0.497
Higher level of negative symptoms	0.98 (0.72-1.32)	0.869	1.12 (0.69-1.81)	0.637	1.60 (1.07-2.39)	0.021	1.21 (0.80-1.84)	0.360

OR – odds ratio

sis at the 20-year reassessment was significantly lower in patients with the *early continuous remission* trajectory (55%) than in those with the *continuous severe symptoms*, *relapse with moderate symptoms* and *stable improvement* trajectories. Remission of negative symptoms (all global SANS scores ≥2) was lower in patients with the *relapse with moderate symptoms* trajectory (9%) than in those with *early continuous remission* and *stable improvement* trajectories (51% and 53%, respectively). The probability of being on antipsychotic medication at the 20-year follow-up was higher for patients with the *continuous severe symptoms* (78%) and the *relapse with moderate symptoms* (80%) trajectories compared with the *early continuous remission* group (48%) (see Table 3).

Negative dimension

Social functioning scores at the 20-year follow-up were significantly higher in patients with the *symptom remission* trajectory (mean PSP score: 65.8, CI: 62.7-68.9) than in those with the *continuous symptoms* trajectory (mean PSP score: 47.7, CI: 44.0-51.4). Patients with the *symptom remission* trajectory had a significantly higher recovery rate (37%) than those with the *continuous symptoms* trajectory (0%). Neurocognitive function was more impaired in patients with the *continuous symptoms* trajectory (z-score: –0.33, CI: –0.53 to –0.13) than in those with the *symptom remission* trajectory (z-score: 0.36, CI: 0.16 to 0.56) (see Table 4).

The number of patients qualifying for a schizophrenia diagnosis at the 20-year reassessment was significantly lower in patients with the *symptom remission* trajectory (50%) than in those with *continuous symptoms* (78%). The probability of being on antipsychotic medication at the 20-year follow-up was significantly higher for patients with the *continuous severe symptoms* trajectory (67%) than in those with *symptoms remission* (36%) (see Table 4).

Table 2 Predictors of membership to negative symptom trajectories using patients with the *symptom remission* trajectory as reference group

	Continuous symptoms	
	OR (95% CI)	p
Male	3.03 (1.48-6.02)	0.002
Finishing high school	0.41 (0.17-1.00)	0.049
Employment	0.83 (0.36-1.88)	0.652
Schizophrenia diagnosis at baseline	2.09 (0.90-4.85)	0.085
Poorer level of premorbid social function	3.27 (0.45-23.84)	0.240
Poorer level of premorbid academic functioning	2.57 (0.28-23.54)	0.403
Longer duration of untreated psychosis	1.01 (1.00-1.02)	0.034
Higher level of global functioning	0.95 (0.92-0.98)	0.001
Higher level of disorganized symptoms	1.52 (0.94-2.44)	0.085

OR – odds ratio

DISCUSSION

This study is the first to explore the trajectories of positive and negative symptoms over the 20-year period following a first psychotic episode in patients with an ICD-10 diagnosis of schizophrenia spectrum disorder.

We found five distinct trajectories of positive symptoms, characterized by *early continuous remission* (50.9%), *stable improvement* (18.0%), *intermittent symptoms* (10.2%), *relapse with moderate symptoms* (11.9%), and *continuous severe symptoms* (9.1%). So, about 69% of the sample did not have sustained positive symptoms. Similarly, in the AESOP 10-year follow-up study[38], an improvement of positive symptoms was observed in 65% of patients. Moreover, in our study, patients with the *intermittent symptoms* trajectory had a mean SAPS score below 2 at the 20-year follow-up, suggesting that the proportion of the sample which did not experience significant positive symptoms at follow-up was close to 80%.

Table 3 Associations between trajectories of positive symptoms and distal outcomes at 20-year follow-up

	Early continuous remission (ECR)	Stable improvement (SI)	Intermittent symptoms (IS)	Relapse with moderate symptoms (RMS)	Continuous severe symptoms (CSS)	p (interclass X^2)	Significant differences between classes ($p<0.05$)
Current treatment with antipsychotics	48%	49%	62%	80%	78%	0.040	ECR vs. RMS and CSS
Current schizophrenia diagnosis	55%	78%	51%	90%	85%	0.002	ECR vs. RMS, CSS and SI
Remission of negative symptoms	51%	53%	22%	9%	30%	0.003	ECR and SI vs. RMS
Clinical recovery	22%	15%	16%	0	0	<0.001	ECR vs. RMS and CSS
Social functioning, mean PSP score (CI)	60.7 (57.6-63.8)	59.0 (52.7-65.3)	44.8 (36.6-53.0)	40.4 (33.4-48.2)	47.9 (40.5-55.3)	<0.001	ECR and SI vs. RMS, CSS and IS
Cognitive function, BACS z-score (CI)	−0.10 (−0.32 to 0.12)	0.31 (−0.06 to 0.68)	0.25 (−0.44 to 0.94)	−0.42 (−1.18 to 0.34)	−0.78 (−1.39 to −0.17)	0.029	CSS vs. ECR, SI and IS

PSP – Personal and Social Performance scale, BACS – Brief Assessment of Cognition in Schizophrenia

Table 4 Associations between trajectories of negative symptoms and distal outcomes at 20-year follow-up

	Symptom remission	Continuous symptoms	p (interclass X^2)
Current treatment with antipsychotics	36%	67%	<0.001
Current schizophrenia diagnosis	50%	78%	<0.001
Remission of negative symptoms	84%	41%	<0.001
Clinical recovery	37%	0%	<0.001
Social functioning, mean PSP score (CI)	65.8 (62.7-68.9)	47.7 (44.0-51.4)	<0.001
Cognitive function, BACS z-score (CI)	0.36 (0.16-0.56)	−0.33 (−0.53 to −0.13)	<0.001

PSP – Personal and Social Performance scale, BACS – Brief Assessment of Cognition in Schizophrenia

However, only the group with *early continuous remission* displayed a significantly higher recovery rate (22%) compared with patients with other trajectories. This finding supports the idea that early remission of positive symptoms is an indicator of a higher chance for recovery, as suggested by other long-term follow-up studies[4,39].

Both patients with the *relapse with moderate symptoms* and the *continuous severe symptoms* trajectories showed a higher probability of being on antipsychotic medication at the 20-year follow-up than patients with other trajectories. This could be interpreted as a sign of treatment resistance. Indeed, these two trajectories accounted for about 20% of patients, similar to the rates of treatment-resistant schizophrenia found in other studies[40,41]. We also found that these two trajectories were associated with lower social and neurocognitive function, and that these patients were less likely to show a remission of negative symptoms. This supports a division of schizophrenia into subgroups based on broader clinical features.

We found that longer duration of untreated psychosis, higher baseline levels of negative symptoms and a diagnosis of substance use disorder predicted membership to less favourable trajectories of positive symptoms. These baseline variables have previously been associated to poor outcome in schizophrenia[42-44]. It is noteworthy that they remain significant predictors of 20-year trajectories. This emphasizes the importance of efforts to reduce the time before patients receive psychiatric treatment (promoting the development of early intervention services), and the need to address substance abuse timely and comprehensively (overcoming the current lack of integration between management of severe mental illness and substance abuse observed in several countries).

We found two trajectories of negative symptoms: *symptom remission* (51.0%) and *continuous symptoms* (49.0%). This finding differs from other studies, all with a follow-up ranging between 1 and 10 years, which identified three or more trajectories, often including one with symptom remission[17,21,45,46]. In one of these studies[21], 85% of patients achieved and maintained low levels of negative symptoms. A meta-analysis also suggested that negative symptoms improve in the vast majority of outpatients after an initial schizophrenia spectrum diagnosis[47]. However, the Suffolk County 20-year follow-up study reported an average increase of negative symptoms over time[14]. So, the longer-time perspective may explain the less favourable scenario observed in our sample. Moreover, according to the criteria suggested by Andreasen et al[26], we regarded symptom levels above 2 on the SANS as defining a *continuous negative symptoms* trajectory. Other studies might have viewed such a level of symptoms as mild and categorized the relevant patients as being in remission.

Baseline predictors associated with membership to the *continuous symptoms* trajectory of negative symptoms were male sex, longer duration of untreated psychosis, lower level of global functioning, and not finishing high school. These baseline variables have previously been associated with poor outcomes in schizophrenia [43,48,49]. We further found the *continuous symptoms* trajectory to be associated with lower social and cognitive functioning at 20-year follow-up. This is in line with research showing that negative symptoms are associated with poor functional outcomes in schizophrenia[50-53]. The clinical recovery rate in the *continuous symptoms* trajectory was 0%, while it was 37% in the *symptom remission* trajectory, emphasizing the urgent need for the development of innovative multimodal interventions for this dimension of schizophrenia spectrum disorder.

The main limitation of this study is the relatively high dropout rate. Conducting long-term follow-up studies in this patient population is difficult, as patients with severe mental illness can be hard to reach. The European data protection law has also restricted the ways patients may be contacted, complicated the matter further. The participants in the 20-year follow-up did not differ from non-participants with respect to any psychopathological variable, including the mean scores on positive and negative dimensions, but they had a slightly but significantly higher level of global functioning at baseline than those lost to follow-up. So, our findings could potentially be biased towards a more positive direction. Moreover, some of the classes of positive symptoms were small in size, which affected power to determine predictors of class membership. Finally, the large time gap between the 10- and 20-year follow-up might have led to an oversimplification of symptom trajectories.

Our analyses are based on a sample of patients originally included in a randomized controlled trial. We know that the interventions impacted differentially on symptom levels for the first two years after inclusion, but we also know that this effect was not seen at any following assessment[22,54,55]. The inclusion of the treatment group in the analyses did not change the results, so we ruled out any significant impact of treatment on the trajectories.

In conclusion, our study is the first to identify 20-year trajectories of positive and negative symptoms after a first psychotic episode in patients with schizophrenia spectrum disorder. We recruited par-

ticipants from both inpatient and outpatient settings, making the study population representative of the real-world schizophrenia spectrum population. Understanding the course of illness can help clinicians inform patients and their families about what can happen after the diagnosis has been made. Identifying different symptom trajectories after the initial diagnosis can improve the way we plan treatment[56,57].

Our study suggests that a high proportion of patients with schizophrenia spectrum disorder recover from positive symptoms, but not from negative symptoms. These latter symptoms are associated with poor functioning and increased mortality[18]. Moreover, negative symptoms may prevent patients from seeking help. This could mean that a subgroup of patients with schizophrenia fall outside the treatment system, because they no longer require treatment for florid symptoms, and negative symptoms prevent them from seeking help for other health issues. The development of innovative multimodal treatment strategies for negative symptoms of schizophrenia spectrum disorder represents today an urgent priority.

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