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Downward clinical course of psychotic disorders during two decades after first hospitalization: Evidence from the Suffolk County Mental Health Project

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Abstract

Objective: Kraepelin considered downward course a hallmark of schizophrenia, but others suggested that outcomes usually stabilize or improve after treatment initiation. We investigated this question in the first U.S. study to follow an epidemiologically-defined cohort with psychotic disorders for 20 years after first hospitalization.

Method: The Suffolk County Mental Health Project recruited first-admission patients with psychosis from all inpatient units of Suffolk County, New York (72% response rate). Participants were assessed in person six times over two decades; 373 completed 20-year follow-up (68% of survivors); 175 had schizophrenia/schizoaffective disorder. Global Assessment of Functioning (GAF), psychotic symptoms, and mood symptoms were rated at each assessment. We used month 6 as a reference, when nearly all participants were discharged from the index hospitalization.

Results: In schizophrenia, mean GAF scores declined from 49 (month 6) to 36 (year 20). Negative and positive symptoms also worsened (Cohen's *d*s = .45 - .73). Other psychoses had higher GAF initially (mean ~64), but it declined by 9 points. Worsening began between years 5 and 8. Neither aging nor changes in antipsychotic treatment accounted for the declines. In all disorders, depression improved and manic symptoms remained low across the 20 years.

Conclusions: We found substantial symptom burden across disorders that increased with time and ultimately may undo initial treatment gains. Previous studies suggested that better health care delivery models may preempt this decline. In the U.S., these care needs are often not met, and addressing them is an urgent priority.

[243 words]

Emil Kraepelin[1] considered declining course a distinguishing feature of schizophrenia (dementia praecox) in contrast to the non-declining, episodic course of mood disorders with psychosis (MoDWP). Others challenged this view, suggesting that a downward trajectory is not typical of schizophrenia and outcomes tend to improve over time[2,3]. Prospective investigations of clinical course—evolution of symptom burden over time—in first episode/admission psychosis (FEP) can provide key evidence for answering this question, as they employ a well-defined early starting point.

Numerous studies followed FEP cohorts in the short- and mid-term. A systematic review found global outcome to be fairly stable across the first decade of illness[4]. Recent 10-year follow-ups of two seminal FEP cohorts observed that positive symptoms initially improve and then stabilize, while negative symptoms remain largely unchanged[5] and only a minority of participants is continuously ill[6]. Overall, this research did not suggest a decline in the first decade of illness, but the second decade may be different.

The international Determinants of Outcome of Severe Mental Disorders (DOSMeD) project is the only prospective study to follow FEP patients for two decades[7,8]. More than half of participants with schizophrenia had good outcome (Global Assessment of Functioning [GAF] score >60), and 50% improved over the interval whereas only 23% declined[8]. However, limited interim information precluded charting of illness trajectories. Also, these analyses included only one small sample *(N* = 56) from the U.S., and large cross-national differences in outcomes were observed[8]. The most similar U.S. project, the Chicago Follow-up Study assessed an early course sample six times over two decades after admission with psychosis. In schizophrenia, global outcome improved through year 7.5 and then stabilized with about 20% having good outcome [9] .

Repeated assessment provided a detailed picture of illness course, but conclusions are limited by a sample drawn primarily from a private hospital.

Less is known about long-term course of MoDWP. The DOSMeD study did not analyze this group separately, but presented all non-schizophrenia psychoses together, finding better outcomes (two-thirds had GAF >60) and course (69% improving and only 12% declining) than in schizophrenia[8]. In the Chicago Follow-up Study, non-schizophrenia psychoses also had better course, with global outcome improving through year 4.5 and then stabilizing with about 40% having good outcome[9]. Another investigation found that only 8% of MoDWP were continuously ill during the decade after first admission[6]. No studies have charted illness trajectories of this group over 20 years.

Furthermore, previous long-term studies largely focused on global outcome and overall pattern of course. Consequently, trajectories of specific symptoms are less understood. At least four clearly distinct dimensions of psychotic symptoms have been identified: reality distortion (i.e., hallucinations, delusions), disorganization, inexpressivity, and apathy-asociality[10,11]. This scheme is an elaboration of the classic 3-dimensional model[12] through division of negative symptoms into apathy-asociality and inexpressivity. Mood symptoms—depression and mania—also play a prominent role in psychotic disorders[13,14]. These six dimensions follow distinct trajectories[15] yet long-term data on changes in many of these symptoms are lacking.

The present study sought to address the aforementioned limitations of long-term follow-up studies of clinical course by: (1) examining an epidemiologically-defined FEP cohort, (2) tracing trajectories of the six symptom dimensions as well as global outcome (GAF) across two decades, (3) following a sufficiently large MoDWP group to precisely chart its course and compare to course of schizophrenia, and (4) using longitudinal consensus diagnoses to define

study groups with high accuracy. The present study is the first to put the four techniques together, offering an unprecedented opportunity to clarify the disagreement between modern views of illness course and Kraepelin's descriptions. Moreover, this also is the first study to attempt direct replication of DOSMeD's long-term findings in the U.S.

Methods

Participants

The cohort was assembled by the Suffolk County Mental Health Project, an epidemiologic study of first-admission psychosis[11,16,17]. Participants were recruited from the 12 psychiatric inpatient units of Suffolk County, NY, 1990-1995. Inclusion criteria were first admission either current or within six months, clinical evidence of psychosis, ages 15-60, IQ >70, proficiency with English, resident of Suffolk County, and no apparent medical etiology. The study was approved annually by the institutional review boards of Stony Brook University and the participating hospitals.

We initially interviewed 675 participants (72% of referrals); 628 of them met the eligibility criteria. Follow-ups were conducted at 6-month, 24-month, 48-month, 10-year, and 20-year points. Seventy nine participants died during the 20 years. Of the 549 survivors, 373 were successfully contacted at year 20 and constitute the analysis sample. Of them, 68.9% lived in Suffolk County, 6.4% moved to another county in NY, and 24.7% moved to another state. Non-participants were similar to the analysis sample on study variables at baseline (demographics, diagnosis, and symptoms; Table 1), but they were less likely to be Caucasian (67.4% vs. 77.7%) and had more severe reality distortion symptoms (Cohen's d = .23). For the analysis sample (N=373), we had 2,046 observations across six waves (i.e., data were 91.4% complete). Follow-ups that were done over the phone (277 across waves) did not allow

behavioral ratings necessary for scoring inexpressivity, resulting in 1,769 observations available for inexpressivity. Primary analyses employed maximum likelihood estimation and thus used all available data.

Measures

Interviews were conducted by master's level mental health professionals. Medical records and interviews with significant others were solicited at every assessment. This multi-source information was used to complete the following rating scales about past-month symptoms: the Scale for the Assessment of Negative Symptoms (SANS [18] the Scale for the Assessment of Positive Symptoms (SAPS[19]) the Brief Psychiatric Rating Scale (BPRS [20] and the Structured Clinical Interview for DSM (SCID [21]) In the present cohort, we scored four reliable factor-analytically derived subscales from the SANS and SAPS: Inexpressivity ($\alpha \geq .88$, 9 items), Apathy-Asociality ($\alpha \geq .81$, 6 items), Reality Distortion ($\alpha \geq .80$, 14 items), and Disorganization ($\alpha \geq .72$, 11 items)[11]. Mania was operationalized with the excitement rating of the BPRS. Depression symptoms were assessed with the current depression module of the SCID administered without skip-outs. We constructed a nine-symptom depression composite (range: 9 – 27) with excellent reliability ($\alpha \geq .81$) and validity[11,17]. All ratings were highly reliable (eMethods).

Primary DSM-IV diagnosis was formulated at the 10-year point by consensus of study psychiatrists using all available information[17]. The same process was performed in previous waves, including 6-month assessment. Diagnoses were grouped into five categories: schizophrenia/schizophreniform/schizoaffective disorder, bipolar disorder with psychosis, depression with psychosis, substance-induced psychosis, and other/undetermined psychosis (e.g.,

psychotic disorder not otherwise specified). Psychiatrists made consensus ratings of the Global Assessment of Functioning (GAF) for the best month of the year before interview, an index that captures both symptoms burden and functional impairment. At year 20, psychiatrists also rated the overall pattern of clinical course following the DOSMeD criteria (see eMethods)[22]. For interpretability, we grouped eight course categories into three: single episode (i.e., baseline episode resolved, no recurrence), multiple episodes, and continuous illness (i.e., no remission).

Data Analysis

We investigated trajectories of each disorder on seven outcome measures: GAF (primary measure) and the six symptom dimensions. All participants were highly symptomatic and hospitalized at baseline; therefore, baseline could not be included in the model and we started charting trajectories from month 6. We focus on mean disorder trajectories here. Within-group heterogeneity was reported previously[11].

First, we examined clinical course in bivariate analyses, comparing outcomes at subsequent follow-ups to month 6 using paired t-tests. We compared outcomes between disorders using independent samples t-tests. Next, we charted trajectories of disorders across all waves by fitting multi-level spline regression models with random intercept (see eMethods)[23-25]. Models were fit for each disorder separately; they estimated trajectories of individual participants and then calculated the mean trajectory for the group. These analyses took advantage of variation in follow-ups around target dates (i.e., some were done late and others early), which allowed us to chart trajectories through year 23. However, data were limited for years 5 – 8 and 13 – 16 (< 20 observations/year) and these portions of trajectories were estimated less precisely. Spline regression is a piecewise regression that allows different slopes in different segments of the predictor variable. We considered up to 3 segments (the largest number suggested by descriptive

analyses). Transition points between segments were determined empirically by testing the full range of possible transition points and selecting the model with the best Bayesian Information Criterion[26]. The number of segments was determined similarly. Finally, we added age and antipsychotic medication as time-varying covariates to resulting models to determine whether observed changes were independent from variation in these covariates.

Results

Description of clinical course

Table 2 shows outcomes and antipsychotic medication use of the five diagnostic groups across the two decades. The pattern is notable for worse outcomes in schizophrenia. Differences among the other groups were less pronounced, although bipolar disorder with psychosis and psychotic depression often had better outcomes than substance-induced and other/undetermined psychoses. Importantly, within-group variability was substantial and often dwarfed between-group differences. The overall pattern of clinical course over 20 years indicated that schizophrenia typically followed a chronic course (74.1% continuously ill), whereas an episodic course was common in bipolar disorder with psychosis (79.5%) and psychotic depression (66.7%), and the other two groups fell between them. Psychotic depression, substance-induced psychosis, and other/undetermined groups were too small (N<50) for planned analyses; therefore, we combined groups based on similarity of course, resulting in three larger categories: schizophrenia (N=175), MoDWP (N=137), and other (N=61).

Next, we tested the significance of changes within the three groups from month 6 to each follow-up (Figure 1). The GAF remained stable or improved from month 6 through 48 for each group, but thereafter declined by 13 points in schizophrenia and 9 points in the other groups.

With regard to specific symptom dimensions, apathy-asociality also remained stable or improved through month 48, but then worsened (*d*s = .35 - .73, comparing year 20 to month 6). Inexpressivity improved through year 10, but by year 20 it returned to initial levels. Reality distortion symptoms were at stable low levels throughout the follow-up in MoDWP and other psychoses. In schizophrenia, reality distortion was stable through month 48, but then increased substantially (*d* = .45), whereas disorganization worsened even more (*d* = .61). These increases are particularly notable given that rates of antipsychotic medication use remained largely stable in schizophrenia, while they declined dramatically in other disorders (eFigure 1). In contrast, depression decreased and mania/excitement remained stable across the interval.

We also compared clinical course among disorders, focusing on the initial outcome (month 6), long-term outcome (year 20), and the change between these waves (eTable 1). Compared to MoDWP, schizophrenia had consistently worse outcomes on GAF, apathy-asociality, inexpressivity, reality distortion, and disorganization. Moreover, worsening was greater in schizophrenia than in MoDWP on these outcomes, except for inexpressivity. No differences were observed between disorders on depression and mania/excitement. The only difference between other psychoses and MoDWP was higher reality distortion symptoms at year 20 in the former.

Although highly accurate, 10-year diagnosis may be confounded by illness course during the first decade. To consider the impact of this confounding, we repeated the analyses using 6-month diagnosis (eFigure 2). Schizophrenia trajectories were virtually unchanged for GAF, apathy-asociality, inexpressivity, reality distortion, and disorganization, whereas MoDWP and other psychoses showed more severe trajectories with 6-month vs 10-year diagnosis. This pattern is consistent with misclassification, namely that some cases who followed schizophrenia

trajectory were assigned other diagnoses at month 6. Indeed, we previously found in this cohort that many 6-month non-schizophrenia cases were later reclassified as schizophrenia, whereas few people shifted out of schizophrenia[17]. The reanalysis with 6-month diagnosis had little impact on trajectories of mood symptoms.

Trajectories of diagnostic groups

Next, we used multi-level spline regression to estimate trajectories of the three groups across the entire follow-up for each outcome. The number of segments was determined empirically (eTable 2). Selected models were either linear (i.e., had only one segment) or allowed one change in trajectory's slope (i.e., had two segments). Estimated trajectories (Figure 2) closely resembled longitudinal patterns obtained by smoothing raw data (eFigure 3), which suggests that models represented the data well. Change per year and its significance are given in Table 3 (unadjusted columns).

GAF declined significantly in schizophrenia; it improved in MoDWP and other psychoses initially, but declined significantly after approximately year 7 (Figure 2). Apathy-asociality worsened in all groups, although in MoDWP it improved through about year 7 and then deteriorated well beyond the initial level. Inexpressivity lessened until approximately year 7 but increased thereafter, except for other psychoses where the trajectory was flat throughout. Reality distortion increased in schizophrenia but remained stable in the other groups. Disorganization worsened in all disorders. Depression improved in all groups, but in MoDWP improvement plateaued at year 2. Mania/excitement did not change significantly across the interval. Changes in GAF were primarily driven by changes in apathy-asociality and reality distortion (eTable 3).

To test whether observed patterns reflect effects of aging or changes in treatment rather than illness evolution, we repeated the analyses controlling for age and antipsychotic use at each assessment point (Table 3). Age had no effect on psychopathology after accounting for time since baseline. Antipsychotic use was associated with worse GAF, inexpressivity, and apathy-asociality overall, but with less disorganization and mania/excitement in schizophrenia. Also, antipsychotic use was associated with lower reality distortion in schizophrenia, but greater symptoms in other psychoses. This pattern may indicate medication side effects or self-selection (e.g., sicker participants are more likely to receive antipsychotics long-term). Adjustment for these two variables did not change findings for illness trajectories except that three slopes became non-significant in other psychoses and two became non-significant in MoDWP. Adjustments for various other potential confounds had little impact on the pattern of results (see eResults and eTable 4).

Discussion

We found that schizophrenia exhibits substantial and consistent decline over the two decades following first hospitalization. Mean GAF score of this group decreased from 49 (at 6-month assessment) to 36 (20-year assessment), and the latter score indicates impairment in reality testing, communication, or pervasive disability. With regard to specific symptom dimensions, worsening was observed in apathy-asociality, reality distortion, and disorganization. MoDWP were less severe than schizophrenia (mean GAF of 65 at 6-month), but they also showed worsening on GAF, apathy-asociality, and disorganization. This decline was smaller (e.g., nine points on GAF) than that in schizophrenia. The decline began five to eight years after the first hospitalization. Depression and mania showed no signs of worsening in any disorders.

Overall, 74% participants with schizophrenia were continuously ill, compared to 14% of MoDWP, and most of the rest of these groups experienced multiple episodes during the 20-year interval.

Our results align with the Kraepelinian view of schizophrenia as following a downward trajectory. The illness worsened gradually, but in the second decade the decline become noticeable. Treatment initiation improved reality distortion and disorganization substantially, as indicated by change from baseline to month 6, but symptoms gradually returned, undoing many treatment gains by year 20. Contrary to Kraepelin's observations, MoDWP also experienced significant worsening, although less pronounced than schizophrenia and limited to negative symptoms (reality distortion and disorganization remained low). Of note, mood symptoms showed a different pattern, either improving or remaining consistently low.

Importantly, heterogeneity within diagnostic groups was substantial, and a number of participants achieved good outcomes (GAF>60 at year 20): 42% of MoDWP, 31% of other psychoses, and 4% of schizophrenia. We previously reported that rank-order stability over 20 years is modest for negative symptoms (test-retest $r \sim .40$) and low for reality distortion and disorganization ($r \sim .20$)[11]. Thus, trajectories of individual participants varied around the mean trend for their group with some increasing and others decrease.

To minimize misclassification, a common problem early in the course of psychosis[17], we used consensus diagnoses based on 10 years of observation. Such diagnoses are very accurate but are influenced by illness course. To examine this confounding, we repeated analyses using 6-month diagnoses. This had little impact on trajectories of schizophrenia, other than moderating the increase of psychotic symptoms somewhat. In contrast, other disorders looked consistently worse when 6 month diagnoses were used. This pattern can be explained by initial

misclassification of schizophrenia cases as non-schizophrenia psychoses. Nevertheless, illness course is integral to diagnostic criteria (e.g., 6 months of symptoms are required for schizophrenia diagnosis) and some circularity is inherent in comparing course of diagnostic groups.

Trajectories of reality distortion were notable in that symptoms worsened in schizophrenia, despite consistently high rates of antipsychotic medication use across the two decades (~80% at each wave). This pattern is consistent with suggestions that antipsychotics may lose some of their effectiveness in the long-term and may even lead to paradoxical effects[27,28] perhaps due to treatment non-adherence and relapses[29]. Also, changes in specific medication prescribed or its dose may contribute to this finding. Our study cannot directly test these possibilities as they require an experimental design.

Present findings paint a bleaker picture than the DOSMeD study, where only 29% of participants with schizophrenia were continuously ill and more than half had GAF>60 after two decades[7]. A variety of factors distinguish the U.S. from other countries included in DOSMeD study (India, Russia, Japan, England, Ireland, and Czech Republic). Availability of family support and community integration may contribute to differences in outcomes[8], but a particularly salient issue is access to treatment. The Suffolk County cohort received community services typical of the U.S. and experienced a substantial unmet need for care[30], which may account for poor outcomes especially compared to countries with universal health care.

On the other hand, our results are consistent with meta-analyses that found outcome in schizophrenia to be almost universally poor [31,32]. Moreover, a systematic review of FEP studies found that during first decade of illness outcomes in treatment studies (mean GAF=66) were much better than in observational studies (mean GAF=50), and the latter are consistent with

initial outcomes in the present cohort. The current study extends these reviews by documenting timing and pace of decline across multiple symptom dimensions.

Our findings are also consistent with evidence of accelerated neurodegeneration in schizophrenia[33] that may underpin worsening negative symptoms. Poor physical health also may contribute to worse clinical course, as it limits daily functioning, impairs cognitive performance, and is common in psychotic disorders[34]. We observed significant effects of poor health in MoDWP but not in other groups (eTable 4). Furthermore, our results for MoDWP are consistent with studies that reported functional impairment and residual symptoms to be very common in psychotic bipolar disorder years after first admission[35].

Current results should not be interpreted as an indication that good outcomes are out of reach. There is extensive evidence that aggressive treatment, especially psychotherapy and vocational rehabilitation, can substantially improve outcomes[36-38]. Moreover, 10-year follow-ups of FEP in Denmark and the United Kingdom, countries with universal access to psychiatric services, found relatively good outcomes with no evidence of decline and few continuously ill participants both in non-schizophrenia and schizophrenia groups[5,6]. It is possible that with better care, outcomes in the U.S. would mirror those of Denmark and the United Kingdom.

This study is the first in the U.S. to follow an epidemiologically-defined large FEP cohort long-term. Nevertheless, it has several limitations. First, it is limited to one geographic location and does not necessarily reflect illness course in other societies. Nevertheless, present findings call attention to a glaring public health problem in the U.S. Second, attrition was non-negligible; 32% of survivors could not be contacted or refused participation. However, attrition analyses suggest that non-participants were largely similar to participants, except for slightly higher likelihood of being a minority and more severe psychotic symptoms at baseline, both risk factors

for worse outcome[29,39]. Thus, the present results may underestimate severity of clinical course. Third, assessments began at first admission rather than first onset. Fortunately, length of pre-admission illness was short relative to the follow-up with median duration of untreated psychosis of 40 days (only 27% were ill for more than a year). Fourth, we did not measure mania symptoms dimensionally and had to rely on a proxy measure, BPRS Excitement. Fifth, the study focused on symptoms and global outcome, and did not consider dimensions of functioning. Functioning was beyond the scope of the present paper focused on symptom burden, but we are reporting several functional outcomes in another publication[40].

Conclusions

Present results suggest an alarming public health problem, a high symptom burden in psychotic disorders that increases with time and ultimately may undo initial treatment gains. Previous studies suggest that better care may preempt this decline. In the U.S., psychotic disorders are associated with a large unmet need for care, and the current study highlights this shortcoming as an urgent priority. Reasons for the decline are unclear and numerous explanations exist. Greater research attention to mid and late course of psychotic disorders is needed to identify factors that drive this decline, just as it unfolds, and learn how to preempt it.

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Table 1. Baseline Characteristics of Follow-up Cohort (N=373) and Surviving Non-Participants (N=176)

	20-Year Cohort N (%)		Non-Participants N (%)		p-value
Demographic characteristics					
Male	222	59.5%	97	55.1%	.329
Age less than 28	195	52.3%	87	49.4%	.533
Blue collar household	165	44.2%	75	42.6%	.721
Race, Caucasian	290	77.7%	119	67.6%	.011
Research diagnosis (last available)					
Schizophrenia spectrum disorders	175	46.9%	73	41.5%	.531
Bipolar I disorder with psychosis	94	25.2%	41	23.3%	
Major depressive disorder with psychosis	43	11.5%	25	14.2%	
Substance-induced psychosis	25	6.7%	16	9.1%	
Other/undetermined psychosis	36	9.7%	21	11.9%	
Baseline Ratings	*Mean*	*(SD)*	*Mean*	*(SD)*	
GAF (best month in year before hospitalization)	58.17	14.25	59.98	14.87	.172
Apathy-asociality	9.38	7.61	8.90	6.21	.435
Inexpressivity	7.32	8.08	6.28	6.98	.142
Reality distortion	10.73	8.71	12.78	10.39	.024
Disorganization	6.89	6.52	6.32	5.89	.321
Depression	17.52	5.38	17.22	4.93	.509
Mania/Excitement	1.66	1.16	1.53	1.07	.192

[a] Surviving nonparticipants were patients who completed baseline assessment but did not participate in the 20-year follow-up assessment and were not known to be deceased: 78 refused, 70 were lost, 15 were impossible to interview (abroad or institutionalized), and 13 provided brief updates insufficient for target ratings. GAF = global assessment of functioning.

Table 2. Characteristics of diagnostic groups over time

Outcome	Schizophrenia		Bipolar disorder with psychosis		Psychotic depression		Substance-induced		Other/ Undetermined	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
GAF										
baseline	52.65	14.17	67.83	9.44	60.30	12.99	57.68	11.92	57.53	14.64
6 months	49.34	13.18	66.37	11.90	61.45	13.94	61.74	11.45	62.73	12.67
24 months	50.39	12.90	69.14	10.83	64.98	12.31	64.65	11.45	60.96	14.39
48 months	49.27	12.21	70.05	11.81	67.93	12.03	65.05	13.06	63.13	15.10
10 years	44.06	10.67	66.95	13.14	65.61	11.72	61.39	13.99	60.93	15.49
20 years	35.79	10.57	57.79	16.78	52.81	16.06	53.88	16.82	51.33	19.03
Apathy-asociality										
baseline	12.11	7.36	4.95	5.74	10.67	7.60	8.40	5.61	6.86	8.26
6 months	11.55	7.92	5.23	6.05	8.51	7.87	7.35	4.98	5.69	7.11
24 months	11.31	6.64	3.76	5.20	6.97	7.32	5.87	5.74	6.36	6.90
48 months	11.30	6.70	3.70	4.67	5.67	6.88	4.47	4.90	7.67	7.12
10 years	13.99	8.14	3.53	4.75	4.60	5.77	7.87	7.96	6.62	8.13
20 years	17.56	8.84	8.00	7.70	10.11	8.52	9.74	9.05	11.51	10.23
Inexpressivity										
baseline	10.22	8.39	3.86	6.10	6.60	8.43	4.28	5.70	5.28	7.23
6 months	10.52	8.92	2.64	4.79	5.00	7.09	3.30	4.20	3.92	6.58
24 months	9.48	8.19	1.80	2.63	3.68	5.62	3.22	5.14	2.68	4.64
48 months	8.82	8.82	1.61	3.15	2.24	3.66	1.53	3.22	3.72	5.30
10 years	7.99	7.67	1.68	3.98	1.87	4.15	2.40	4.57	2.83	6.49
20 years	10.32	10.37	3.69	5.45	4.26	7.13	4.00	6.17	7.90	11.34
Reality distortion										
baseline	12.54	9.36	10.77	8.87	6.23	6.00	8.40	6.89	8.83	6.05
6 months	4.26	7.44	0.56	1.29	2.81	4.56	1.52	3.19	2.50	4.67
24 months	4.41	6.36	0.99	3.19	0.92	2.74	1.83	3.66	3.40	6.30
48 months	4.03	6.67	1.05	2.78	0.94	2.52	1.53	3.01	3.44	7.96
10 years	6.66	8.24	0.46	1.86	1.03	2.29	1.78	3.25	3.07	5.69
20 years	7.31	9.34	0.84	2.16	0.93	2.32	2.73	4.79	3.47	5.92
Disorganization										
baseline	7.19	7.00	8.97	6.05	1.86	2.96	5.68	5.37	6.89	6.07
6 months	2.99	5.14	1.61	3.00	0.89	1.37	0.70	1.15	2.08	2.64
24 months	2.99	4.35	2.19	3.93	1.08	2.13	2.09	3.63	3.36	5.22
48 months	3.65	4.87	2.34	4.22	0.73	1.86	0.47	1.02	2.33	3.07
10 years	4.27	6.00	1.79	3.74	0.94	2.45	1.29	2.24	3.64	6.20
20 years	6.16	7.28	3.21	5.22	2.45	4.33	2.07	3.76	5.71	6.32
Depression										
baseline	17.04	5.02	16.85	5.13	22.21	5.23	16.96	5.83	16.42	5.10
6 months	13.55	4.03	12.13	3.35	15.51	5.51	12.70	3.97	13.04	5.08

24 months	13.20	4.46	11.16	3.47	12.86	5.27	12.52	4.67	13.72	5.00
48 months	10.69	3.79	9.94	3.07	12.00	5.72	10.53	3.42	11.72	5.38
10 years	11.92	3.76	10.99	3.47	13.35	5.10	12.55	4.27	11.37	3.25
20 years	11.60	3.28	11.87	3.93	13.35	4.57	11.43	3.51	12.45	3.85
Mania/Excitement										
baseline	1.49	1.00	2.13	1.39	1.07	0.34	1.96	1.34	1.78	1.22
6 months	1.21	0.66	1.44	0.90	1.00	0.00	1.26	0.75	1.20	0.71
24 months	1.22	0.65	1.41	0.92	1.14	0.48	1.22	0.60	1.48	1.08
48 months	1.33	0.68	1.47	0.96	1.12	0.42	1.21	0.54	1.39	0.78
10 years	1.29	0.80	1.35	0.90	1.15	0.48	1.57	1.20	1.59	1.37
20 years	1.28	0.83	1.34	0.87	1.13	0.47	1.14	0.48	1.21	0.63
	N	%	N	%	N	%	N	%	N	%
Use antipsychotics										
baseline	152	86.9%	82	87.2%	31	72.1%	15	60.0%	31	86.1%
6 months	148	84.6%	63	67.0%	24	55.8%	9	36.0%	20	55.6%
24 months	136	79.5%	37	39.4%	18	41.9%	4	16.7%	14	40.0%
48 months	122	70.1%	32	34.0%	10	23.3%	4	16.0%	12	33.3%
10 years	142	87.1%	34	40.0%	8	20.0%	6	26.1%	7	25.9%
20 years	117	81.8%	30	36.1%	10	25.0%	4	20.0%	10	37.0%
Illness pattern over 20 years										
Single episode	1	0.6%	10	11.4%	8	19.0%	4	17.4%	10	38.5%
Multiple Episodes	43	25.3%	70	79.5%	28	66.7%	13	56.5%	8	30.8%
Continuous illness	126	74.1%	8	9.1%	6	14.3%	6	26.1%	8	30.8%

Note: For apathy-asociality, inexpressivity, reality distortion, and disorganization scales, zero indicates no symptoms; depression scale ranges from 9 (no symptoms) to 27; mania/excitement range from one (none) to seven (very severe). Sample size for symptom outcomes is N = 153, 148, 145, 166, and 175 for schizophrenia (6-month to 20-year wave, respectively); 83, 81, 82, 86, and 94 for bipolar disorder with psychosis; 38, 41, 40, 41, and 43 for psychotic depression; 26, 28, 23, 29, and 36 for substance-induced psychosis; and 23, 23, 21, 23, and 25 for other/undetermined psychoses.

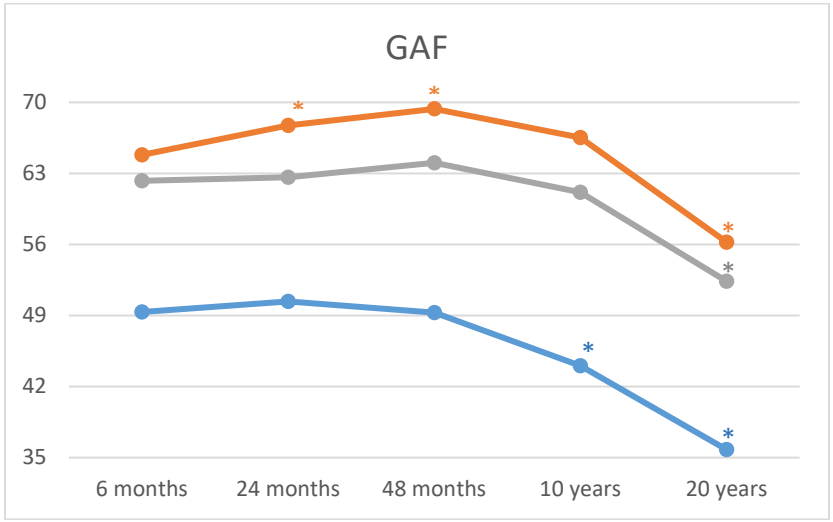
Table 3. Changes in symptoms over time: unadjusted and adjusting for age and antipsychotic medications

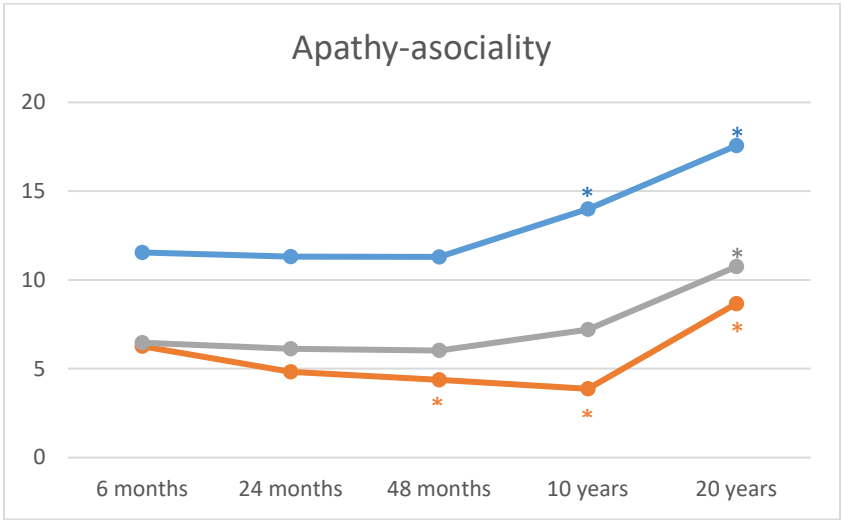
	Schizophrenia				MoDWP				Other Psychoses			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	p-value	B	p-value	B	p-value	B	p-value	B	p-value	B	p-value
GAF												
Time(S1)	-0.70	<.001*	-0.59	<.001*	1.52	<.001*	1.26	<.001*	0.49	.119	0.60	.097
Time(S2)	---	---	---	---	-0.98	<.001*	-0.94	<.001*	-0.99	<.001*	-0.60	.011
Age	---	---	-0.10	.231	---	---	-0.07	.415	---	---	-0.31	.055
Antipsychotics	---	---	-0.84	.480	---	---	-4.78	<.001*	---	---	-5.19	.004*
Apathy-asociality												
Time(S1)	0.34	<.001*	0.26	<.001*	-0.59	<.001*	-0.58	<.001*	0.22	<.001*	0.05	.571
Time(S2)	---	---			0.48	<.001*	0.40	<.001*	---	---	---	---
Age	---	---	0.09	.133	---	---	0.09	.014	---	---	0.16	.045
Antipsychotics	---	---	2.59	.001*	---	---	2.33	<.001*	---	---	1.90	.058
Inexpressivity												
Time(S1)	-0.51	<.001*	-0.55	<.001*	-0.45	<.001*	-0.29	.019	0.12	.035	0.11	.245
Time(S2)	0.27	<.001*	0.32	.002*	0.23	<.001*	0.21	<.001*	---	---	---	---
Age	---	---	0.00	.957	---	---	-0.02	.453	---	---	0.01	.912
Antipsychotics	---	---	2.59	.003*	---	---	2.04	<.001*	---	---	1.98	.035*
Reality distortion												
Time	0.18	<.001*	0.20	.003*	-0.02	.102	-0.04	.056	0.03	.299	-0.04	.553
Age	---	---	-0.02	.679	---	---	0.02	.124	---	---	0.07	.208
Antipsychotics	---	---	-1.82	.027	---	---	0.54	.020	---	---	2.24	.001*
Disorganization												
Time	0.18	<.001*	0.18	.001*	0.07	<.001*	0.05	.064	0.11	.001*	0.03	.602
Age	---	---	-0.01	.875	---	---	0.02	.393	---	---	0.07	.146
Antipsychotics	---	---	-1.65	.005*	---	---	0.00	.990	---	---	-0.05	.939
Depression												
Time(S1)	-0.10	<.001*	-0.08	.016	-0.99	.001*	-0.89	.002*	-0.06	.065	-0.15	.007*
Time(S2)	---	---	---	---	0.03	.166	0.00	.969	---	---	---	---

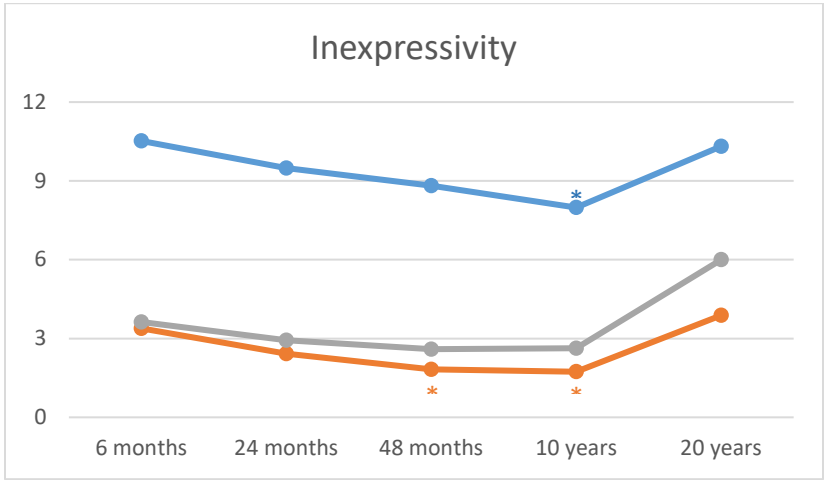
Age	---	---	-0.02	.466	---	---	0.04	.130	---	---	0.08	.056
Antipsychotics	---	---	0.72	.088	---	---	0.83	.033	---	---	1.49	.019
Mania/Excitement												
Time	0.00	.313	0.01	.149	0.00	.696	0.00	.887	0.00	.889	-0.01	.368
Age	---	---	-0.01	.291	---	---	0.00	.549	---	---	0.01	.332
Antipsychotics	---	---	-0.20	.009*	---	---	0.09	.229	---	---	0.02	.896

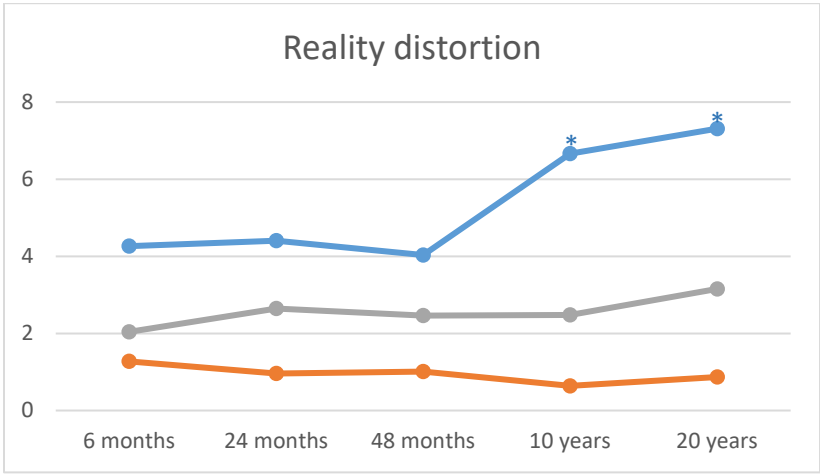
Note: B = change in symptom score per year; dashes indicate non-applicable (i.e., effects not included in the model). MoDWP = mood disorder with psychosis. S1 is first segment of the 20-year interval or the entire interval, if we model has only one segment; S2 is the second segment. Transition point between segments for GAF was at year 5 in MoDWP and year 7 in other psychoses; for apathy-asociality it was at year 7 in MoDWP; for inexpressivity it was at year 6 in MoDWP and year 7 in schizophrenia; for depression it was at year 2 in MoDWP.
Sample size is $N = 175$ for schizophrenia, 137 for MoDWP, and 61 for other psychoses.
*p <.01

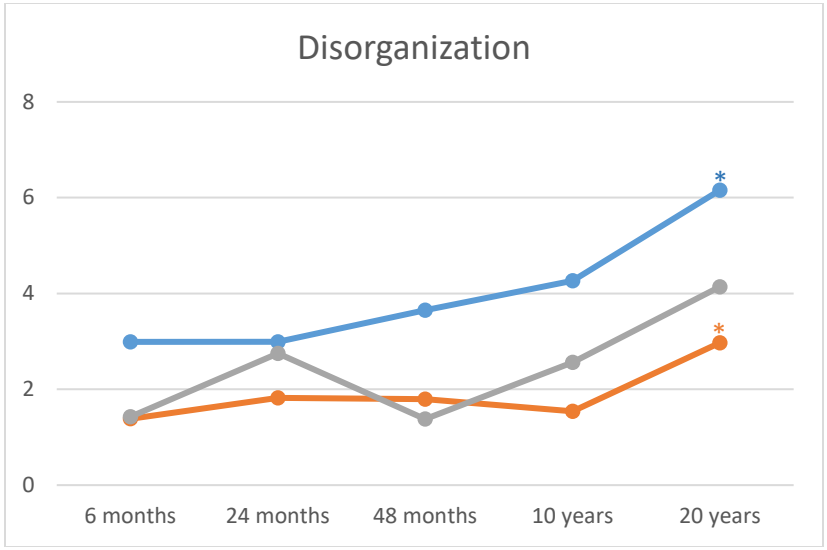
Figure 1. Outcomes in major diagnostic groups: means at each follow-up and comparison to month 6

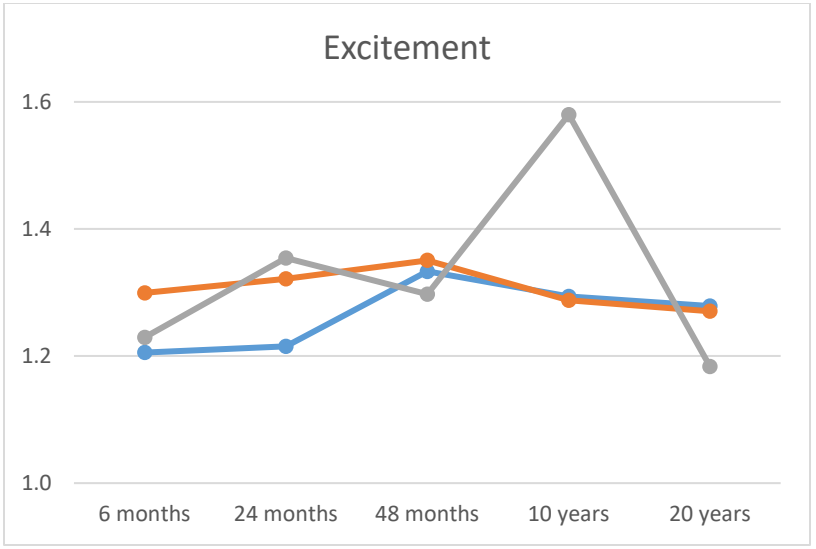


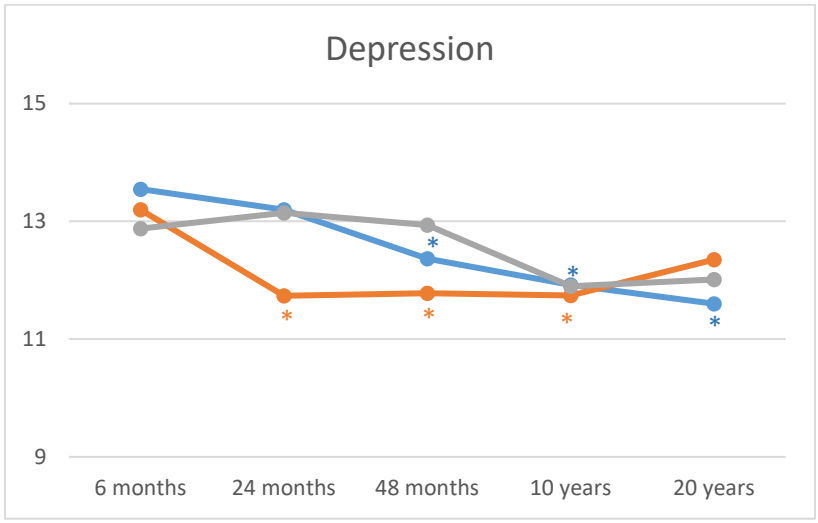






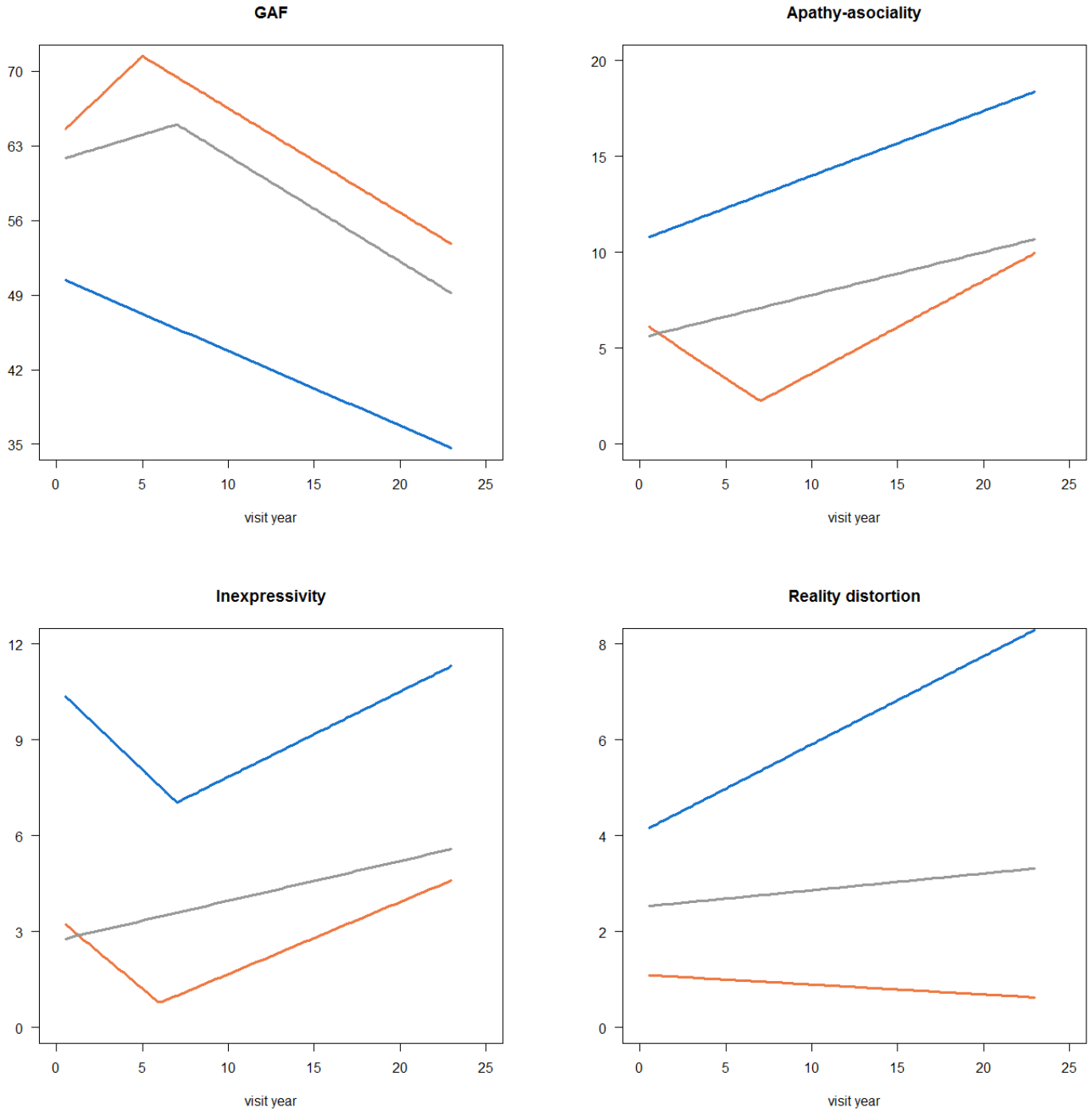


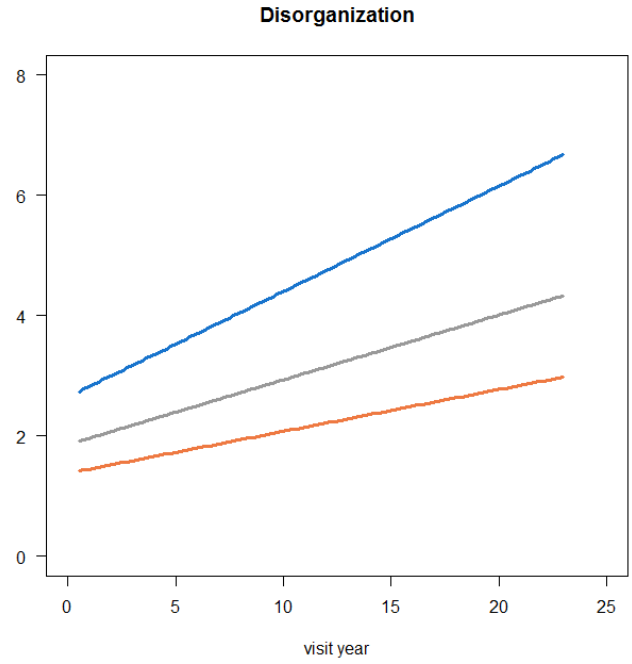


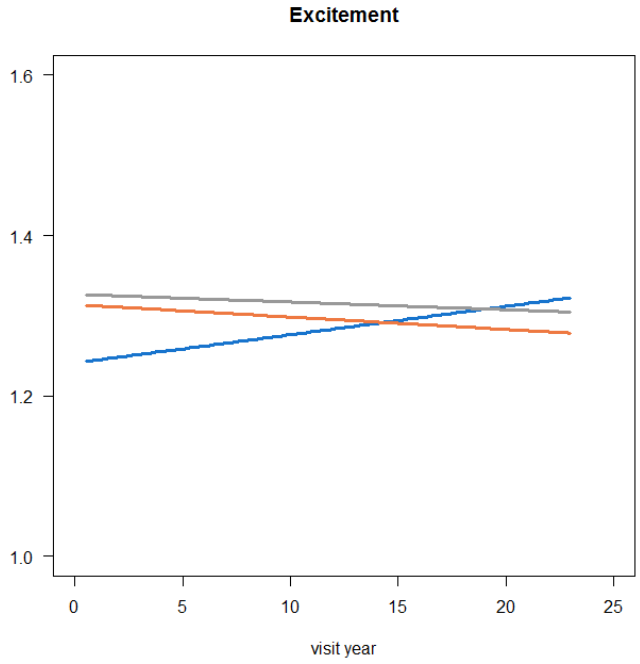


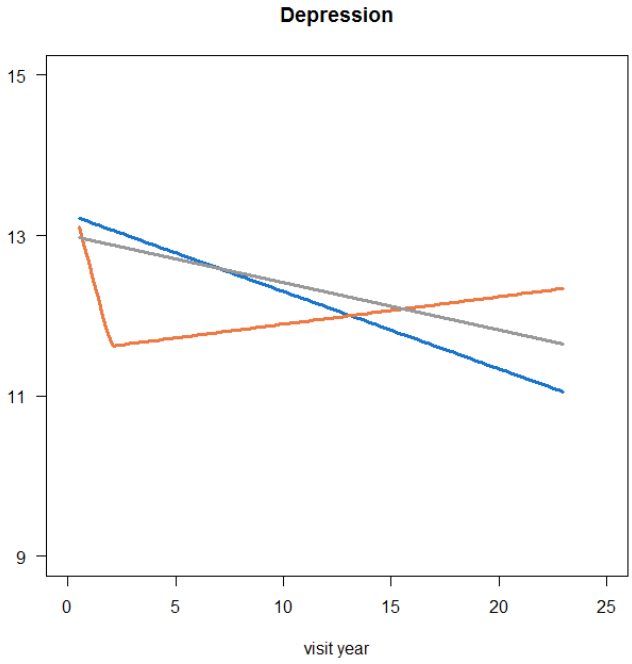
Note: Blue = schizophrenia, orange = mood disorders with psychosis, grey = other psychoses.
Sample size is *N* = 153, 148, 145, 166, and 175 for schizophrenia (6-month to 20-year wave, respectively), 121, 122, 122, 127, and 137 for MoDWP, and 49, 51, 44, 52, and 61 for other psychoses.
*p<.01 for difference between 6-month and a later follow-up

Figure 2. Trajectories of diagnostic groups post-admission modeled using spline regression









Note: Blue line is schizophrenia, orange line is mood disorders with psychosis, grey line is other psychoses

Sample size is *N* = 175 for schizophrenia, 137 for MoDWP, and 61 for other psychoses.

eMethods

DOSMeD rating of overall pattern of clinical course considers both psychotic and mood symptoms. The rating consists of eight mutually exclusive categories[22]:

1. single psychotic episode followed by full symptom remission
2. single psychotic episode followed by incomplete remission
3. single psychotic episode followed by one or more non-psychotic episodes, with full symptom remissions between all or most of the episodes.
4. single psychotic episode followed by one or more non-psychotic episodes, with incomplete remissions between all or most of the episodes.
5. two or more psychotic episodes, with full symptom remissions between all or most of the episodes.
6. two or more psychotic episodes, with incomplete remissions between all or most of the episodes.
7. continuous psychotic illness (no remission):
8. continuous non-psychotic illness (no remission); psychotic symptoms may have been present for some time but non-psychotic symptoms predominate throughout.

Due to small number of cases in some of the categories, we aggregated eight categories into three common patterns: single episode (categories 1 and 2), multiple episodes (categories 3, 4, 5 and 6), and continuous illness (categories 7 and 8).

The BPRS Excitement rating reflects affective core of mania, but does not capture associated symptoms. Interviewers are instructed to rate "heightened emotional tone, including irritability and expansiveness (hypomanic affect)." Rating scale ranges from 0 (not observed) to 7 (very severe).

As reported previously, reliability of ratings from baseline to year 10 was excellent with intraclass correlations $\geq .75$[11,16,17]. At year 20, interviewers rated 30 randomly selected audio recordings of 10-year interviews to evaluate consistency between waves. Intraclass correlations were .94 for Apathy-Asociality, .97

for Reality Distortion, and .93 for Disorganization, .96 for BPRS Excitement, and .87 for SCID Depression. Inexpressivity could not be rated from audio recordings.

Multi-level spline regression was used to estimate outcome trajectories of the diagnostic groups from month 6 to year 20. This model describes individual trajectory of each participant in terms of starting level (intercept) and subsequent progression (captured by slope in each segment). Intercept was modeled as a random effect (parameter that varies between people). Since change may be non-linear, we compared two-segment spline models (i.e., trajectory is continuous but has one slope in the first segment and a different slope in the second segment) to single-segment models (consistent change throughout the entire follow-up). In the two-segment model, transition between segments was determined empirically by selecting time point for transition that maximized model fit. Model selection was done in each diagnostic group independently. After a spline model was selected, we estimated mean trajectory for the group and calculated significance of slopes to test for change in the outcome over time. Next, we added time-varying covariates to the model (e.g., age, medication) to determine whether changes in these variables explain changes in an outcome over time. Analyses were performed in in SAS version 9.2 with PROC GLIMMIX.

eResults

Although focus of the study is on trajectories of symptoms, we thought it informative to also describe patterns of medication use over time (eFigure 1). Antipsychotics were used at a consistently high rate (~80%) in schizophrenia group, other than a small reduction at year 10; while use of antipsychotics declined substantially in MoDWP (from 63% at month 6 to 32% at year 20), and other psychoses showed a similar decline but it did not reach statistical significance. In contrast, use of antidepressants and mood stabilizers remained unchanged in all groups from month 6 to year 20, except for a small increase in mood stabilizer use in schizophrenia (from 15% to 25%).

We examined six additional time-varying covariate that might explain slopes of trajectories: (1) hospitalizations (annual rate in the interval preceding the assessment), (2) number of medical conditions the participant reported being treated for or diagnosed with during the interval (assessed with the chronic conditions module of the Composite International Diagnostic Interview[41], which includes diabetes, hypertension, other heart problems, gastrointestinal problems, asthma, arthritis, cancer, liver problems, thyroid problems, headaches, seizures, eye problems, hearing problems, and HIV), (3) major depressive episode in the interval (assessed with the SCID[21]), (4) manic episode in the interval (assessed with the SCID[21]), (5) number of medication visits to a mental health provider (monthly rate averaged across six months prior to the assessment), and (6) number of psychotherapy visits (monthly rate averaged across six months prior to the assessment). Data were obtained by interviews with participants, interviews with significant others, and review of medical records when available.

These variables were added to spline regression models that controlled for age and antipsychotic use, resulting in eight time-varying covariates altogether. Simultaneous adjustment for these covariates generally did not alter the course of the seven outcomes in the three diagnostic groups, except that increase in apathy-asociality became non-significant in other psychoses after controlling for psychotherapy visits, initial decrease in inexpressivity became non-significant in MoDWP after controlling for antipsychotics, increase in disorganization was fully explained in MoDWP by occurrence of manic episodes and hospitalizations in the interval, and decrease in depression became non-significant in schizophrenia and MoDWP after controlling for occurrence of major depressive episodes in the interval (eTable 4). Thus, even controlling for a range of covariates, we observed a global decline (indicated by the GAF) in all groups and an increase in

psychosis specific to schizophrenia. This suggests that the downward clinical course observed in this cohort is not due to aging, mood episodes, physical comorbidities, or changes in treatment, although our ability to test treatment effects is limited by the observational nature of the study.

[41]Kessler, R. C., & Üstün, T. B. (2004). The world mental health (WMH) survey initiative version of the world health organization (WHO) composite international diagnostic interview (CIDI). International journal of methods in psychiatric research, 13(2), 93-121.

eTable 1. Differences between disorders at month 6, year 20, and in change from month 6 to year 20

	MoDWP			Other Psychoses				Schizophrenia			
	N	M	SD	N	M	SD	p-value	N	M	SD	p-value
GAF											
6mo	121	64.83	12.73	49	62.27	12.00	.229	153	**49.34**	13.18	.000
20yr	137	56.23	16.66	61	52.37	18.05	.144	175	**35.79**	10.57	.000
20yr-6mo	121	-8.86	15.72	49	-8.64	17.16	.933	153	**-13.19**	14.08	.017
Inexpressivity											
6mo	117	3.38	5.70	49	3.63	5.55	.797	146	**10.52**	8.92	.000
20yr	93	3.88	6.03	39	6.00	9.29	.195	129	**10.32**	10.37	.000
20yr-6mo	84	0.33	7.15	31	3.39	10.10	.073	111	0.44	10.84	.933
Apathy-asociality											
6mo	117	6.26	6.82	49	6.47	6.20	.857	146	**11.55**	7.92	.000
20yr	128	8.67	8.00	51	10.75	9.68	.178	149	**17.56**	8.84	.000
20yr-6mo	110	2.58	7.97	41	4.19	8.58	.280	126	**6.13**	8.86	.001
Reality distortion											
6mo	117	1.27	2.95	49	2.04	4.03	.233	146	**4.26**	7.44	.000
20yr	128	0.87	2.20	52	**3.15**	5.44	.005	151	**7.31**	9.34	.000
20yr-6mo	110	-0.40	3.42	42	1.00	4.80	.089	126	**3.77**	11.47	.000
Disorganization											
6mo	117	1.38	2.61	49	1.43	2.17	.917	146	**2.99**	5.14	.001
20yr	126	2.97	4.96	51	4.14	5.62	.173	148	**6.16**	7.28	.000
20yr-6mo	110	1.76	5.51	41	1.87	4.61	.910	124	**3.79**	7.20	.016
Depression											
6mo	117	13.20	4.42	49	12.88	4.55	.675	146	13.55	4.03	.502
20yr	124	12.35	4.18	49	12.01	3.70	.625	141	11.60	3.28	.111
20yr-6mo	106	-0.96	5.30	40	-0.97	4.21	.991	118	-1.90	4.54	.154
Excitement											
6mo	117	1.30	0.77	48	1.23	0.72	.590	146	1.21	0.66	.290
20yr	122	1.27	0.77	49	1.18	0.57	.476	147	1.28	0.83	.932
20yr-6mo	105	0.00	1.03	39	-0.05	0.89	.783	126	0.13	0.87	.281

Note: p-values reflect t-tests comparing schizophrenia and other psychoses to mood disorders with psychosis (MoDWP). Bold indicates statistically significant differences ($p < .05$).

eTable 2. Fit of spline models

segments	Schizophrenia		MoDWP		Other	
Symptom	BIC	ΔBIC	BIC	ΔBIC	BIC	ΔBIC
GAF						
1	**5603**	--	4533	--	1912	--
2	5596	7	**4483**	50	**1901**	11
3	5589	7	4479	3	1896	4
Apathy-asociality						
1	**4772**	--	3745	--	**1537**	--
2	4767	6	**3710**	35	1534	3
3	4760	6	3706	3	1533	1
Inexpressivity						
1	4600	--	3057	--	**1377**	--
2	**4586**	14	**3040**	16	1373	5
3	4579	7	3039	2	1369	4
Reality distortion						
1	**4870**	--	**2701**	--	**1373**	--
2	4869	1	2701	0	1372	1
3	4866	2	2702	-2	1372	0
Disorganization						
1	**4226**	--	**3023**	--	**1300**	--
2	4226	0	3022	1	1301	0
3	4224	1	3020	2	1300	1
Depression						
1	**3749**	--	3205	--	**1309**	--
2	3744	4	**3191**	14	1308	1
3	3743	1	3191	-1	1307	1
Mania/Excitement						
1	**1502**	--	**1326**	--	**589**	--
2	1504	-2	1329	-3	585	4
3	1507	-3	1332	-3	584	2

Note: BIC = Bayesian Information Criterion. Bold indicates selected model (less parsimonious model was selected if it improved BIC by at least 10 points). Analyses were stratified by primary diagnosis. MoDWP = mood disorders with psychosis. Sample size is *N* = 175 for schizophrenia, 137 for MoDWP, and 61 for other psychoses.

eTable 3. Changes in symptoms explain contemporaneous changes in GAF

	Schizophrenia		MoDWP		Other Psychoses	
	β	p-value	β	p-value	β	p-value
Inexpressivity	**-0.11**	.0005	**-0.11**	.0005	0.00	.9965
Apathy-asociality	**-0.45**	<.0001	**-0.49**	<.0001	**-0.53**	<.0001
Reality distortion	**-0.25**	<.0001	**-0.05**	.0414	**-0.29**	<.0001
Disorganization	**-0.18**	<.0001	**-0.08**	.0195	-0.07	.1521
Depression	**0.07**	.0167	-0.02	.5919	-0.02	.6760
Excitement	**0.09**	.0081	**-0.06**	.0441	-0.03	.5355

To evaluate contributions of individual symptoms to global outcome, we constructed a multi-level model (with random intercept and slopes) for GAF regressed on the six symptom dimensions treated as time-varying predictors. The predictors entered the model simultaneously. All predictors were converted to z-scores prior to analysis to ensure comparability of effect sizes. Sample size is $N = 175$ for schizophrenia, 137 for MoDWP, and 61 for other psychoses.
$p < .05$ effects are bolded.

eTable 4. Changes in symptoms over time: unadjusted and adjusting for eight time-varying covariates

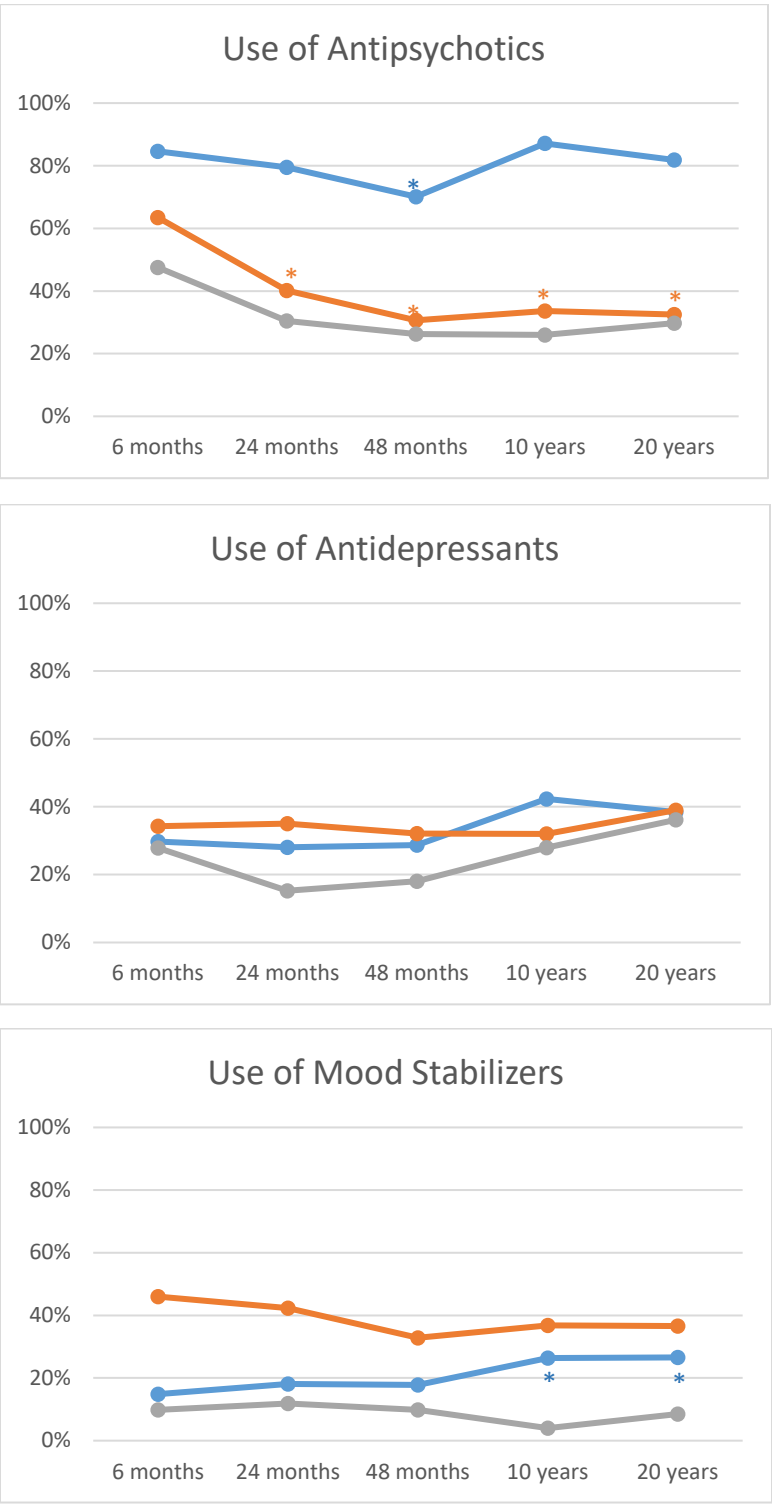
	Schizophrenia				MoDWP				Other Psychoses			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	p-value	B	p-value	B	p-value	B	p-value	B	p-value	B	p-value
GAF												
Time(S1)	-0.7	<.001*	-0.56	<.001*	1.52	<.001*	0.89	.006*	0.49	.119	0.59	.145
Time(S2)	---	---	---	---	-0.98	<.001*	-0.93	<.001*	-0.99	<.001*	-0.70	.007*
Age	---	---	-0.11	.215	---	---	0.01	.938	---	---	-0.27	.113
Antipsychotics	---	---	-0.93	.485	---	---	-4.00	<.001*	---	---	-4.99	.016
Hospitalizations	---	---	-0.64	.346	---	---	-1.41	.006*	---	---	-0.34	.764
Physical conditions	---	---	-0.48	.275	---	---	-1.82	<.001*	---	---	0.04	.954
MDE	---	---	0.03	.978	---	---	-0.63	.500	---	---	0.91	.627
Manic episode	---	---	4.40	.013	---	---	1.16	.334	---	---	3.32	.372
Medication visits	---	---	0.45	.456	---	---	-0.55	.438	---	---	-0.89	.515
Psychotherapy visits	---	---	0.16	.516	---	---	0.02	.952	---	---	-0.01	.987
Apathy-asociality												
Time(S1)	0.34	<.001*	0.24	.001*	-0.59	<.001*	-0.43	.002*	0.22	<.001*	0.09	.342
Time(S2)	---	---	---	---	0.48	<.001*	0.40	<.001*	---	---	---	---
Age	---	---	0.10	.105	---	---	0.06	.109	---	---	0.12	.116
Antipsychotics	---	---	2.43	.003*	---	---	2.16	<.001*	---	---	1.06	.323
Hospitalizations	---	---	0.22	.584	---	---	0.65	.041	---	---	0.62	.318
Physical conditions	---	---	0.28	.322	---	---	0.98	<.001*	---	---	0.60	.142
MDE	---	---	-0.58	.430	---	---	0.25	.664	---	---	1.25	.218
Manic episode	---	---	0.73	.500	---	---	-0.66	.348	---	---	-1.77	.382
Medication visits	---	---	0.40	.278	---	---	0.21	.611	---	---	0.22	.777
Psychotherapy visits	---	---	-0.13	.394	---	---	0.11	.525	---	---	0.64	.006*
Inexpressivity												
Time(S1)	-0.51	<.001*	-0.56	<.001*	-0.45	<.001*	-0.24	.072	0.12	.035	0.15	.095
Time(S2)	0.27	<.001*	0.35	.002*	0.23	<.001*	0.24	<.001*	---	---	---	---
Age	---	---	0.02	.767	---	---	-0.03	.345	---	---	-0.01	.847
Antipsychotics	---	---	2.80	.003*	---	---	2.04	<.001*	---	---	1.54	.153
Hospitalizations	---	---	0.56	.238	---	---	0.48	.056	---	---	1.39	.031
Physical conditions	---	---	-0.25	.434	---	---	0.13	.473	---	---	0.46	.264

MDE	---	---	-1.25	.147	---	---	0.17	.710	---	---	-0.61	.575
Manic episode	---	---	-2.04	.111	---	---	-0.74	.196	---	---	-0.91	.666
Medication visits	---	---	0.27	.509	---	---	-0.06	.858	---	---	0.48	.544
Psychotherapy visits	---	---	-0.05	.774	---	---	-0.07	.606	---	---	0.11	.646
Psychosis												
Time	0.18	<.001*	0.20	.005*	-0.02	.102	-0.05	.019	0.03	.299	-0.02	.759
Age	---	---	-0.03	.609	---	---	0.01	.381	---	---	0.05	.363
Antipsychotics	---	---	-1.42	.116	---	---	0.26	.315	---	---	2.01	.006*
Hospitalizations	---	---	0.44	.341	---	---	0.28	.046	---	---	0.86	.039
Physical conditions	---	---	0.46	.125	---	---	0.36	<.001*	---	---	0.35	.185
MDE	---	---	-0.17	.837	---	---	0.62	.012	---	---	-0.40	.550
Manic episode	---	---	1.84	.129	---	---	0.48	.111	---	---	2.94	.030
Medication visits	---	---	-1.14	.006*	---	---	-0.14	.451	---	---	-0.51	.303
Psychotherapy visits	---	---	0.03	.866	---	---	0.01	.941	---	---	-0.17	.278
Disorganization												
Time	0.18	<.001*	0.16	.004*	0.07	<.001*	0.00	.978	0.11	.001*	0.05	.290
Age	---	---	-0.01	.814	---	---	0.03	.151	---	---	0.03	.488
Antipsychotics	---	---	-1.23	.021	---	---	-0.51	.167	---	---	-0.02	.972
Hospitalizations	---	---	0.16	.541	---	---	0.60	.001*	---	---	0.81	.027
Physical conditions	---	---	0.18	.363	---	---	0.10	.468	---	---	0.14	.539
MDE	---	---	-0.57	.222	---	---	-0.14	.689	---	---	-0.02	.969
Manic episode	---	---	1.00	.150	---	---	1.65	<.001*	---	---	4.13	<.001*
Medication visits	---	---	-0.50	.036	---	---	-0.34	.185	---	---	-0.87	.049
Psychotherapy visits	---	---	-0.01	.946	---	---	0.11	.311	---	---	0.11	.428
Depression												
Time(S1)	-0.1	<.001*	-0.07	.027	-0.99	.001*	-0.45	.145	-0.06	.065	-0.12	.030
Time(S2)	---	---	---	---	0.03	.166	-0.05	.177	---	---	---	---
Age	---	---	-0.01	.655	---	---	0.02	.277	---	---	0.03	.408
Antipsychotics	---	---	0.87	.044	---	---	0.19	.629	---	---	1.20	.070
Hospitalizations	---	---	0.14	.552	---	---	0.11	.614	---	---	-0.16	.696
Physical conditions	---	---	0.19	.175	---	---	0.65	<.001*	---	---	0.74	.003*
MDE	---	---	3.11	<.001*	---	---	2.25	<.001*	---	---	4.08	<.001*
Manic episode	---	---	1.47	.013	---	---	1.21	.010	---	---	-0.47	.726
Medication visits	---	---	-0.29	.147	---	---	0.23	.424	---	---	-0.22	.657

Psychotherapy visits	---	---	0.12	.137	---	---	0.21	.071	---	---	-0.06	.701
Mania/Excitement												
Time	0.00	.313	0.00	.427	0.00	.696	-0.01	.111	0.00	.889	-0.01	.561
Age	---	---	-0.01	.277	---	---	0.00	.822	---	---	0.00	.703
Antipsychotics	---	---	-0.15	.054	---	---	0.02	.755	---	---	-0.04	.785
Hospitalizations	---	---	0.02	.592	---	---	0.06	.144	---	---	0.01	.918
Physical conditions	---	---	0.02	.529	---	---	0.02	.413	---	---	-0.02	.725
MDE	---	---	-0.09	.221	---	---	-0.09	.227	---	---	0.02	.869
Manic episode	---	---	0.12	.247	---	---	0.35	<.001*	---	---	0.59	.026
Medication visits	---	---	-0.08	.023	---	---	-0.01	.855	---	---	-0.16	.103
Psychotherapy visits	---	---	0.00	.826	---	---	-0.01	.688	---	---	0.00	.932

Note: B = change in symptom score per year. Dashes indicate non-applicable (i.e., effects not included in the model). MoDWP = mood disorder with psychosis. S1 is first segment of the 20-year interval or the entire interval, if we model has only one segment; S2 is the second segment. Transition point between segments for GAF was at year 5 in MoDWP and year 7 in other psychoses; for apathy-asociality it was at year 7 in MoDWP; for inexpressivity it was at year 6 in MoDWP and year 7 in schizophrenia; for depression it was at year 2 in MoDWP. Unadjusted results are the same as in Table 3 and are included for reference to help interpret impact of covariates on trajectories. Sample size is $N = 175$ for schizophrenia, 137 for MoDWP, and 61 for other psychoses.
*p <.01

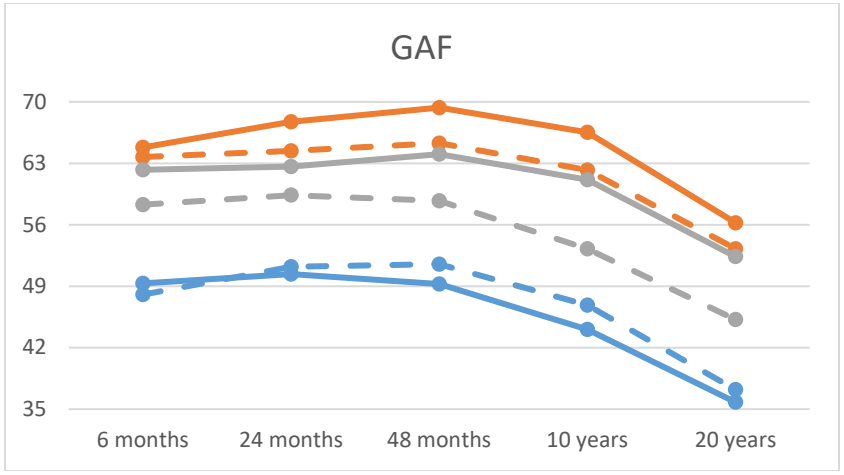
eFigure 1. Antipsychotics, antidepressants, and mood stabilizers in major diagnostic groups: prevalence at each follow-up and comparison to month 6

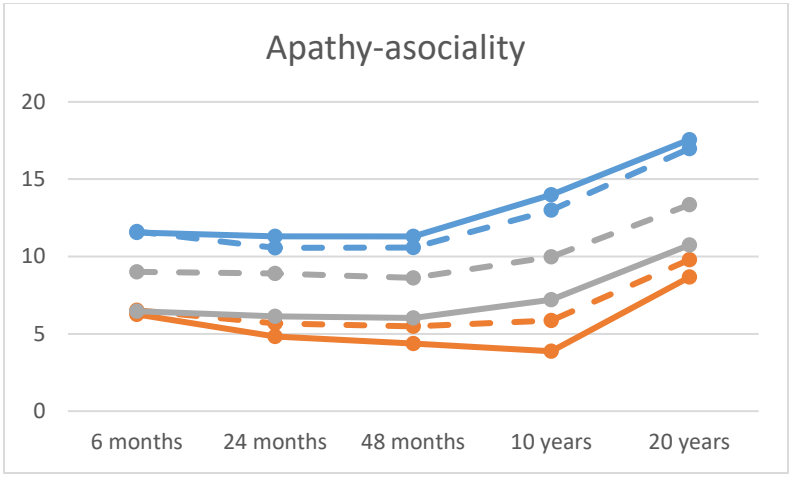


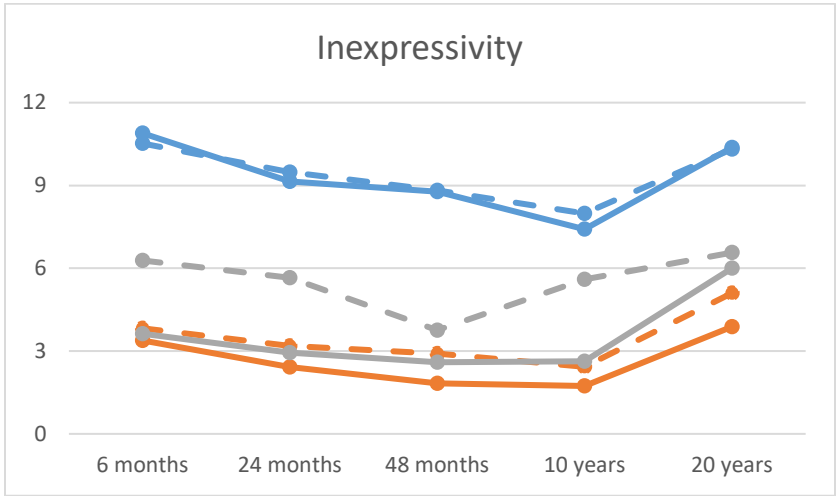
Note: Blue = schizophrenia, orange = mood disorders with psychosis, grey = other psychoses. Sample size is *N* = 175, 171, 174, 163, and 143 for schizophrenia (6-month to 20-year wave, respectively), 137, 137, 137, 125, and 123 for MoDWP, and 61, 59, 61, 50, and 47 for other psychoses.

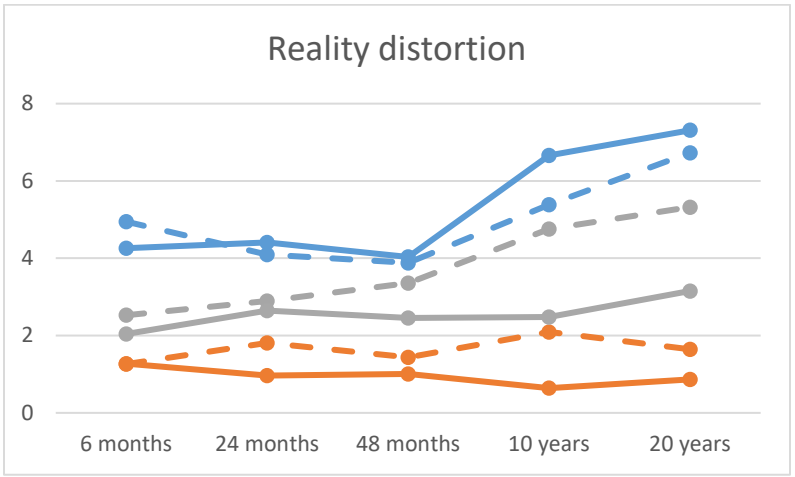
*p<.01 for difference between 6-month and a later follow-up

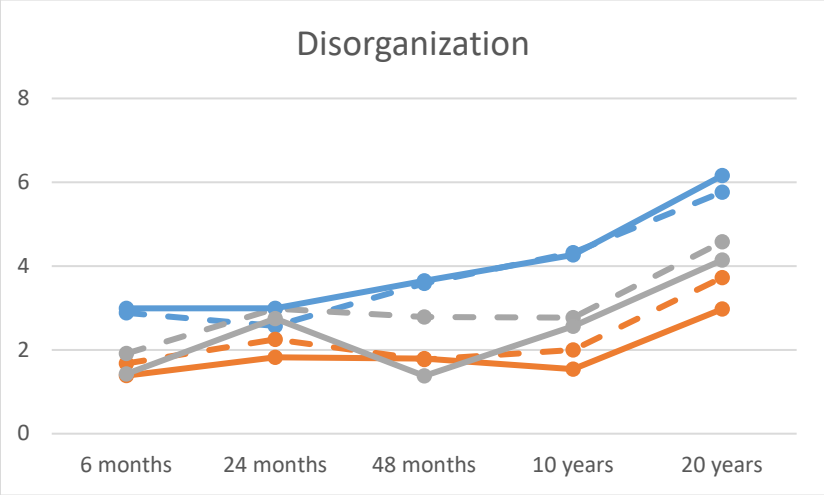
eFigure 2. Mean outcomes in major groups for 6-month and 10-year diagnoses

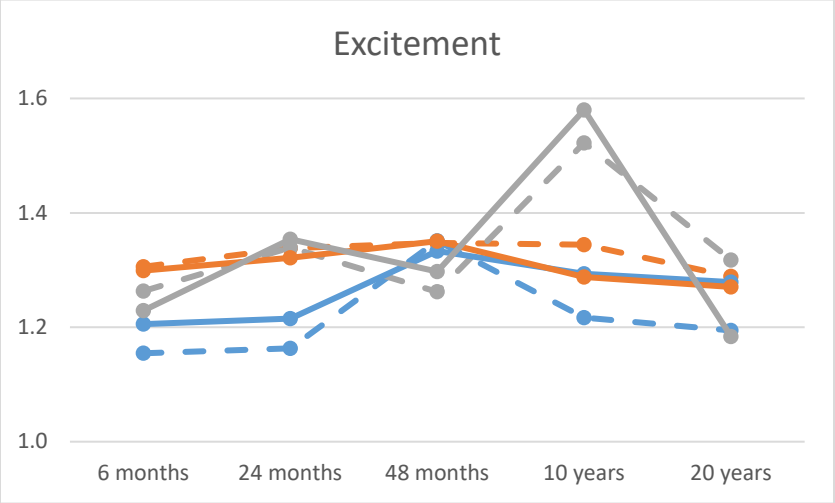


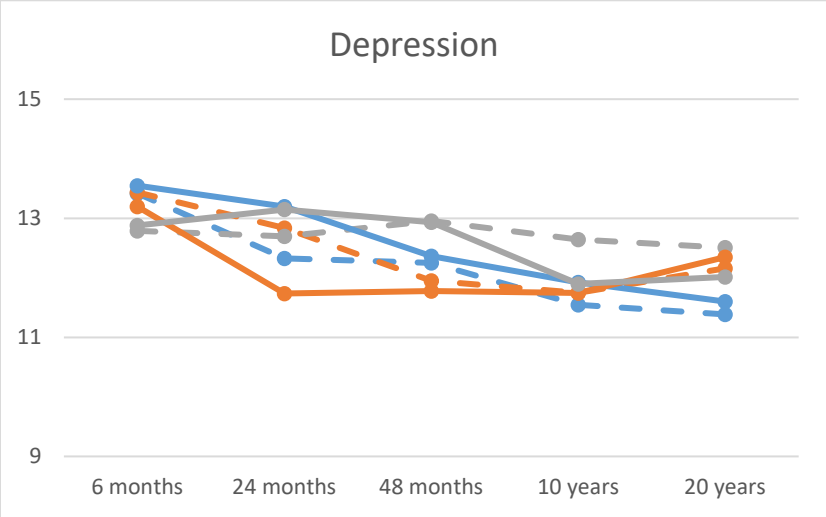






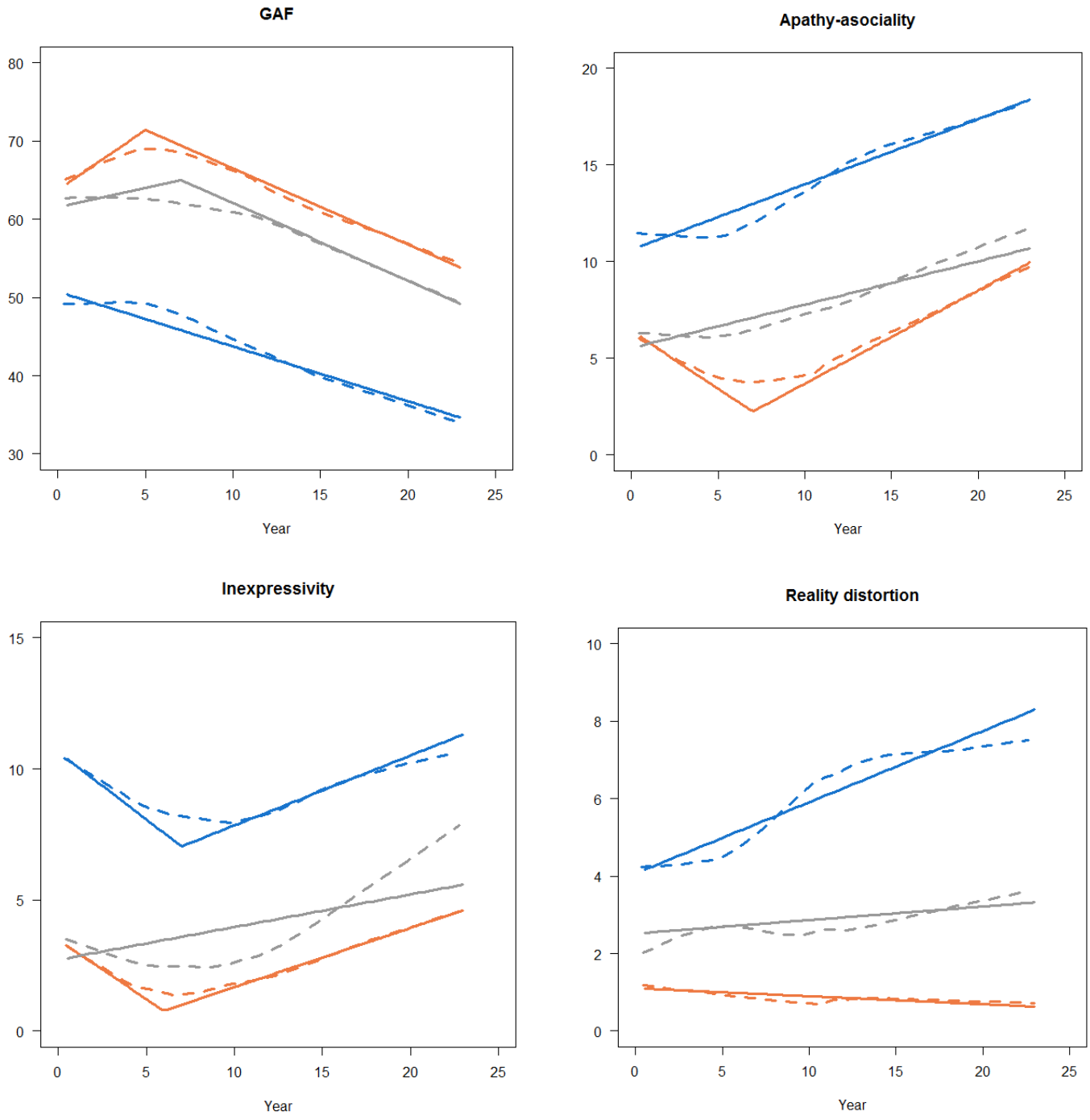


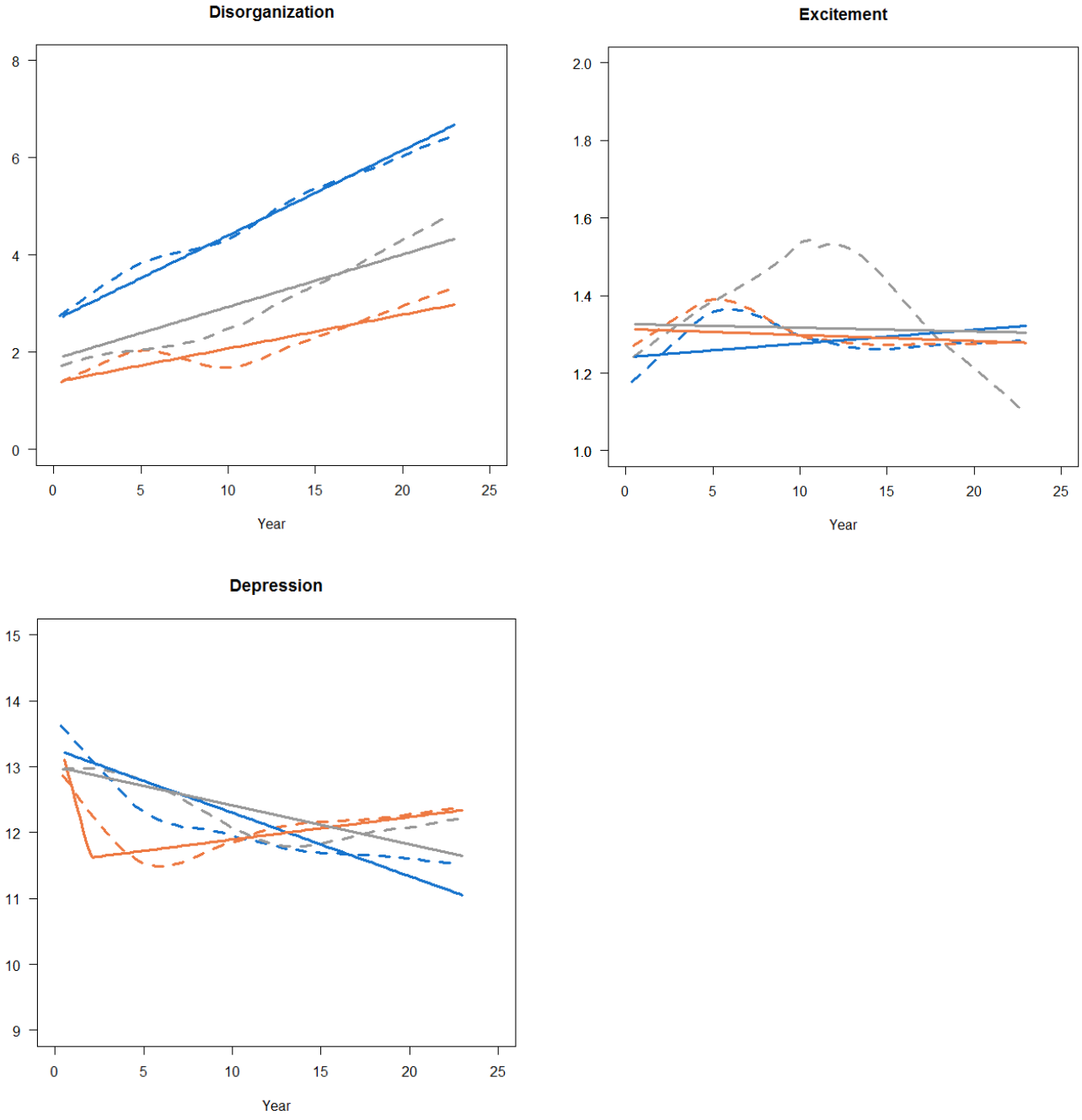




Note: To evaluate confounding of 10-year diagnosis with illness course, we compared trajectories for the three disorder groups defined according to 10-year diagnosis (solid lines) to groups defined by 6-month diagnosis (dashed lines). Blue = schizophrenia, orange = mood disorders with psychosis, grey = other psychoses. Sample size is *N* = 115, 110, 111, 124, and 129 for 6-month schizophrenia (6-month to 20-year wave, respectively), 147, 149, 146, 152, and 165 for 6-month MoDWP, and 61, 62, 54, 69, and 79 for 6-month other psychoses. Sample size is *N* = 153, 148, 145, 166, and 175 for 10-year schizophrenia (6-month to 20-year wave respectively), 121, 122, 122, 127, and 137 for 10-year MoDWP, and 49, 51, 44, 52, and 61 for 10-year other psychoses.

eFigure 3. Comparison of trajectories from spline regression to smoothing of raw data





Note: To evaluate accuracy of the multi-level spline regression models, we compared these models to smoothing data with locally weighted scatterplot smoothing (LOESS). LOESS uses weighted least squares to fit linear functions within a fixed neighborhood of each data point. It was applied for each diagnostic group separately. Solid lines are modeled curves from Figure 2. Dashed lines are LOESS curves. Blue = schizophrenia, orange = mood disorders with psychosis, grey = other psychoses. Sample size is *N* = 175 for schizophrenia, 137 for MoDWP, and 61 for other psychoses.