

1 **Original article**

2 **Mediators of quality of life change in people with severe psychotic disorders**  
3 **treated in integrated care (ACCESS II study)**

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39 **ABSTRACT**

40 **Background:** Patients with severe psychotic disorders exhibit a severely reduced quality of life (QoL)  
41 at all stages of the disease. Integrated Care often led to an improvement in QoL. However, the specific  
42 mediators of QoL change are not yet well understood.

43 **Methods:** The ACCESS II study is a prospective, long-term study investigating the effectiveness of an  
44 Integrated Care program for people with severe psychotic disorders (IC-TACT) that includes Therapeu-  
45 tic Assertive Community Treatment within a care network of in- and outpatient services at the Univer-  
46 sity Medical Center Hamburg-Eppendorf, Germany. We examined longitudinal associations between  
47 QoL and the hypothesized mediators of change (i.e. negative symptoms, depression and anxiety), using  
48 cross-lagged panel models.

49 **Results:** The sample includes 418 severely ill patients treated in IC-TACT for at least one year. QoL  
50 increased while symptom severity decreased significantly from baseline to 6-months follow-up ( $p$ -val-  
51 ues  $\leq 0.001$ ), and remained stable until 12-months follow-up. QoL and symptom severity demonstrated  
52 significant auto-correlated effects and significant cross-lagged effects from QoL at baseline to negative  
53 symptoms (6 months,  $\beta = -0.20$ ,  $p < 0.001$ ) to QoL (12 months,  $\beta = -0.19$ ,  $p < 0.01$ ) resulting in a significant  
54 indirect, mediated effect. Additionally, negative symptoms after 6 months had a significant effect on  
55 severity of depression after 12 months ( $\beta = 0.13$ ,  $p < 0.05$ ).

56 **Conclusions:** Negative symptoms appear to represent an important mechanism of change in IC-TACT  
57 indicating that improvement of QoL could potentially be achieved through optimized intervention on  
58 negative symptoms. Moreover, this may lead to a reduction in severity of depression after 12 months.

59

60 **Key words:** Schizophrenia, bipolar disorder, severe mental illness, quality of life, patient-reported out-  
61 come, assertive community treatment, integrated care

62

**63 1. Introduction**

64 Quality of life (QoL) has become an important issue in the care of people with mental illness. Major  
65 reasons include the increasing community-based and patient-centered care, the importance of sub-  
66 jective well-being, and the acceptance of QoL as an important criterion for treatment success (1). Alt-  
67 hough there is no universal definition of QoL, it is generally accepted that it contains both objective  
68 (e.g., mental and physical health) and subjective (e.g., feeling of well-being and satisfaction) dimen-  
69 sions (2,3).

70 Patients with psychotic disorders, especially those diagnosed with schizophrenia or those who meet  
71 the criteria for severe mental illness (SMI), exhibit a severely reduced quality of life at all stages of the  
72 disease. Systematic reviews and meta-analyses have shown that patients at risk for the development  
73 of psychosis (4) and during the early (5) and long-term phase (6) have a reduced QoL. The main medi-  
74 ating factors comprise poor mental and physical health, depression, anxiety, severity of illness, coping,  
75 problems in social relationships, and environmental domains such as living circumstances or finances  
76 (6).

77 Evidence-based care including evident care models (Early Intervention Services, EIS; (7–9), Assertive  
78 Community Treatment (ACT; (10) including evident treatment components (e.g., pharmacotherapy,  
79 cognitive-behavioral therapy, social and somatic interventions; (7,9,11) often led to an improvement  
80 in QoL. However, with regard to mental health as one of the key factors affecting QoL, the specific  
81 mechanism of change that make ACT effective with regard to QoL are not yet well understood (12).

82 The identification of such mediators (mechanisms) of change requires the study of intervening varia-  
83 bles that account for the effect of a specific treatment, such as IC-ACT, on the outcome of interest (12).

84 Possible mediators linking the treatment content to the improvement on QoL are levels of anxiety,  
85 depression and negative symptoms as these have been demonstrated to respond to IC-ACT (8,13,14)  
86 and to be associated with QoL (6), both cross-sectionally and longitudinally (6).

87 In line with these results, a recent study demonstrated that treatment-induced effects of IC-TACT on  
88 QoL after 12 months were mediated by changes in anxiety, depressive and negative symptoms (12).  
89 More precisely, changes in QoL were achieved by two pathways: One pathway leading from changes  
90 in negative symptoms to depressive symptoms and a second one through changes in anxiety. However,  
91 in the cited study change scores of all mediators and QoL between baseline and follow-up assessment  
92 were used. This does not allow any conclusion about the temporal order between these variables  
93 which is inherently postulated in a mediation model, i.e., anxiety, depressive and negative symptoms  
94 are predictive of QoL and not vice versa. Thus, it is required to investigate both mediators and outcome  
95 variable (QoL) at repeated measures over time to disentangle cause and effect by taking reciprocal  
96 effects into account. Additionally, such a procedure would provide a more fine-grained understanding  
97 of potential mechanisms of change of ACT as it also allows to disentangle the effects of mediators by  
98 investigating at which time-point a mediator exerts its largest effect on other mediators as well as on  
99 the outcome of interest (15).

100 Another limitation refers to the fact that most studies investigating mechanisms of change of ACT so  
101 far used standard regression procedures not taking the stability of symptom levels and QoL over time  
102 into account. This may have led to an overestimation of the longitudinal association between two var-  
103 iables due to the high stability of these constructs in terms of high auto-correlations across time. Fur-  
104 thermore, these results may have been biased by not taking cross-sectional associations between  
105 symptom levels and QoL measured at the same time-point into account.

106 This may have led to an overestimation of the longitudinal association between two variables due to  
107 the high stability of these constructs in terms of high auto-correlations across time. Furthermore, these  
108 results may have been biased by not taking cross-sectional associations between symptom levels and  
109 QoL measured at the same time-point into account.

### 110 **1.1. Aims of the study**

111 To address the aforementioned limitations, in this study we examined the prospective, reciprocal as-  
112 sociations between negative symptoms, depression, anxiety and QoL at three prospective assessment-  
113 points (baseline, 6 months, 12 months) in a sample of patients with a severe psychotic disorder cur-  
114 rently being treated with integrated care including a high fidelity variation of assertive community  
115 treatment, so-called Therapeutic Assertive Community Treatment (TACT). Analyses were carried out  
116 using cross-lagged panel models within the structural equation modeling framework (16) to test the  
117 hypothesis that QoL after 12 months is predicted by anxiety, depression and negative symptoms while  
118 controlling for the stability of and cross-correlations between these constructs. Additionally, we hy-  
119 pothesized that the beneficial effect on QoL is mediated by negative symptoms, depressive symptoms  
120 and anxiety.

## 121 **2. Materials and methods**

### 122 *2.1. Context*

123 ACCESS is an integrated care program for people with non-affective and affective severe psychotic  
124 disorders that incorporates Therapeutic Assertive Community Treatment (TACT) within a multi-sec-  
125 toral and interdisciplinary care network of inpatient and outpatient providers (8,11,17). The effective-  
126 ness of the ACCESS program was assessed within three studies so far: the ACCESS I study assessed the  
127 implementation of the model (10,14); the ACCESS II study assesses all patients entering the program  
128 since the approval by health insurances in Germany (11,17,18); the ACCESS III study evaluated the  
129 effectiveness of the expansion of the model to adolescent (from the age of 12 years) and young adult  
130 patients in the early stage of the illness (8).

### 131 *2.2. Study design and sample*

132 The ACCESS II study is a prospective, single center, ongoing, long-term study assessing the effective-  
133 ness and efficiency of the so-called “*Hamburg Model of Integrated Care (ACCESS)*” for people with  
134 severe psychotic disorders (8,11,14,17–20). It investigates the long-term effectiveness of the identi-  
135 cally named integrated care model ACCESS in a patient group diagnosed with affective or non-affective

136 psychotic disorders also meeting the severe and persistent mental illness (SPMI) criteria. The ACCESS  
137 program is ongoing, 433 patients entered the program in the here studied enrollment period from May  
138 2007 to September 2019. Those who participated in the program for at least one year ( $n = 418$ ; 96,5  
139 % of the total enrollment) were included in the analysis. The trial was approved by the local ethics  
140 committee (number: PV4059) and is registered at ClinicalTrials.gov (identifier: NCT01888627).

### 141 *2.3. Inclusion and Exclusion Criteria*

142 Inclusion criteria for the study are (i) aged 12 years or older, (ii) presence of one of the following diag-  
143 noses according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; (21)): schiz-  
144 ophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder  
145 not otherwise specified, bipolar disorder most recent severe with psychotic symptoms, and major de-  
146 pression, single or recurrent, severe with psychotic symptoms; (iii) written informed consent by the  
147 patient ( $\geq 18$  years) or by guardians with written informed assent by patient (12-17 years). Exclusion  
148 criteria comprised (i) presence of one of the following diagnoses according to DSM-IV-TR: Alcohol- or  
149 substance-induced psychosis (comorbid alcohol or substance abuse or dependence were tolerated),  
150 psychotic disorder due to a medical condition, and mental disability.

### 151 *2.4. Assessments and measures*

152 Assessments were carried out at baseline, week 6, and months 3, 6, and thereafter every 6 months (13  
153 examination times) by trained raters. All diagnoses were assessed as follows: (a) psychosis and comor-  
154 bid mental disorders with the German version of Structured Interview I and, if indicated II for DSM-IV  
155 (22); chronic somatic disorders, social support diagnoses (Z-diagnosis), and suicide attempt diagnoses  
156 with the ICD-10-GM (23). Demographic characteristics were assessed with the Early Psychosis File  
157 Questionnaire (EPFQ; (24), psychopathology with the Brief Psychotic Rating Scale (BPRS; (25). Here,  
158 item 2 of the BPRS was used to measure severity of anxiety and item 3 for severity of depression. Item  
159 13 (self-neglect), item 16 (blunted affect), item 17 (emotional withdrawal) and item 18 (motor retar-  
160 dation) were used to form a summary score of these 4 negative symptoms according to (26). Further,

161 functional level was assessed with the Global Assessment of Functioning Scale (GAF; (21)), severity of  
162 illness for schizophrenia spectrum disorders with the Clinical Global Impressions Scale-Schizophrenia  
163 (CGI-Sch; (27)), severity of illness for bipolar disorder (affective psychosis) with the CGI-Bipolar Disor-  
164 der (CGI-BP; (28)), quality of life with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-  
165 LES-Q-18; (29)). The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18; (29)) is a  
166 self-report instrument developed for patients with schizophrenia to assess their satisfaction with sev-  
167 eral life domains. Each of its 18 items is rated on a 5-point Likert scale ranging from 'not at all or never'  
168 to 'frequently or all the time' depending on how often a person reports aspects of the QoL questions.  
169 Higher values indicate better QoL. In order to evaluate the questionnaire, the mean value is formed  
170 over all 18 items. The subscales (physical health, subjective feelings, leisure time active ties and social  
171 relationships) are also evaluated by forming means (and standard deviations). In order to make the  
172 results easier to interpret and comparable, the mean values were transformed to a value range from  
173 0-100 with higher values being associated with a higher self-reported quality of life.

#### 174 *2.5. Statistical analyses*

175 Analyses were performed with SPSS version 25 and Mplus version 8.0 (30). Descriptive analyses con-  
176 sisted of frequencies in categorical variables and means and standard deviations (SDs) for continuous  
177 variables. Bivariate correlations among model variables were calculated across the three time-points  
178 (baseline (T0), 6 months (T1), 12 months(T2)).

179 Effect sizes were expressed as correlation coefficients and Cohen's *d* for pre-post, pre-follow-up, and  
180 post-follow-up assessments ( $(M_{\text{post}} - M_{\text{pre}})/SD_{\text{pre}}$ ) for the descriptive analyses, and standardized partial  
181 regression coefficients for the cross-lagged panel models. Cohen's cut offs for small, medium, and large  
182 effects were set at  $\geq 0.2$ ,  $0.5$ , and  $0.8$  respectively. Similarly, for correlation analyses correlation coef-  
183 ficients of  $\geq 0.1$ ,  $0.3$ , and  $0.5$  were used to indicate weak, moderate, and strong correlations, respec-  
184 tively.



185 Cross-lagged panel models based on the three assessment-points (baseline (T0), 6 months (T1), 12  
186 months (T2)) were calculated to investigate the longitudinal relationships between negative symp-  
187 toms, depressive symptoms, anxiety and QoL. These models allow estimating the reciprocal relation-  
188 ships between model variables by using earlier measures of a construct to predict later measures of  
189 another construct (i.e., cross-lagged association). Simultaneously, the stability of each construct is es-  
190 timated by regressing earlier measures of a construct on later measures of a construct (i.e., autoregres-  
191 sive effect) (31). Residual variances were allowed to correlate at same assessment-points. The signifi-  
192 cance of the indirect effect was tested by calculating bootstrapped, bias-corrected confidence-inter-  
193 vals with 1000 iterations of the indirect effect. Missing values were handled with use of Full Infor-  
194 mation Maximum Likelihood (FIML). Model fit was assessed by the Comparative Fit Index (CFI), the  
195 Tucker-Lewis index (TLI), and the Root-Mean-Square Error of Approximation (RMSEA). A good-fitting  
196 model should produce CFI- and TLI-values higher than 0.95, and a RMSEA-value lower than 0.05.

### 197 **3. Results**

#### 198 *3.1. Sociodemographic and illness characteristics at baseline*

199 Sociodemographic and illness characteristics at baseline of the 418 patients are displayed in table 1.  
200 Both genders were almost equally represented in the patient cohort (47.8% male, 52.2% female). Over  
201 two thirds (70.1%) were diagnosed with non-affective psychosis. Schizophrenia was the most frequent  
202 diagnosis (60.3%), followed by Bipolar I disorder (14.8%) and schizoaffective disorder (13.6%). 27.5%  
203 were included during their first episode, whereas 72.5% had already experienced at least one or mul-  
204 tiple prior episodes. Concurrent with meeting the severe mental illness (SMI) criteria, patients dis-  
205 played high scores of psychopathology (BPRS mean = 78.47%), severity of illness (CGI-S total mean =  
206 5.53, SD = .93) and low functioning level (GAF mean = 39.51, SD = 12.48), as well as low QoL-related  
207 scores (Q-LES-Q-18 total mean = 36.98, SD = 17.99) at baseline.

208 =====

209 Please include table 1 about here!

210 =====

211 Table 2 shows the BPRS and Q-LES-Q-18 baseline and changes scores over 1-year in level of total psy-  
212 chopathology, negative symptoms, depression, anxiety, and quality of life. Over the first 6 months,  
213 there was a highly significant improvement in overall psychopathology, negative, depressive and anx-  
214 iety symptoms and QoL. The effect was small to medium for negative and depressive symptoms  
215 ( $d=0.39-0.63$ ), and large for overall psychopathology, anxiety and QoL (total score, anxiety and QoL:  
216  $d=1.11$  to  $1.36$ ). Between 6-months and 12-months follow-up level of symptomatology and QoL did  
217 not change significantly.

218 =====  
219 Please include table 2 about here!  
220 =====

### 221 3.2. Correlations between model variables

222 As shown in table 3, model variables were significantly correlated with effect sizes ranging between  
223 weak ( $0.11$ ) and strong ( $0.69$ ). Exceptions mainly involved level of anxiety. In detail, no significant as-  
224 sociations were found for anxiety at baseline with negative symptoms (6 months and 12 months), de-  
225 pression and QoL (12 months) as well as between anxiety at 6-months follow-up and severity of nega-  
226 tive symptoms at baseline. Further, QoL at baseline was not significantly associated with severity of  
227 depression at 6-months follow-up.

228 =====  
229 Please include table 3 about here!  
230 =====

### 231 3.3. Results of the cross-lagged panel model

232 The cross-lagged panel model (see Figure 1) showed an excellent fit to the data as indicated by the  
233 following fit indices: CFI= $0.99$ , TLI= $0.97$  and RMSEA= $0.04$  ( $0.00$ ;  $0.07$ ;  $p=0.59$ ). QoL, negative  
234 symptoms, depression and anxiety were all stable across time as indicated by significant auto-  
235 regression coefficients between  $0.22$  for QoL (T0-T1) to  $0.69$  for negative symptoms (T1-T2). All

236 associations were stronger between 6 and 12 months (T1-T2) than between baseline and 6-month  
 237 follow-up (T0-T1). QoL at baseline significantly predicted negative symptoms at 6-month follow-up,  
 238 which predicted improvements in QoL at 12-month follow-up. This indirect, mediated effect was  
 239 significant (95% CIs of standardized IE= 0.01; 0.08,  $p=0.03$ ). Improvements in both QoL and negative  
 240 symptoms after 6 months significantly predicted improvements in depression at 12-month follow-up.  
 241 The indirect effect from QoL at baseline to depression at 12-month follow-up through improvements  
 242 of negative symptoms was small and reached only a trend-level (95% CIs of standardized IE= -0.07; -  
 243 0.01,  $p=0.08$ ). The same applied to the indirect effect of QoL at baseline and after 6 months on  
 244 depression after 12 months (95% CIs of standardized IE= -0.07; -0.01,  $p=0.07$ ). Anxiety could only be  
 245 predicted by previous levels of anxiety, but had no significant association with any other model  
 246 variable.

247 =====  
 248 Please include figure 1 about here!  
 249 =====

## 250 4. Discussion

251 The ongoing ACCESS II trial assesses the effectiveness of the integrated care model, including TACT for  
 252 people with severe psychotic disorders fulfilling established SMI criteria (8,11,17,19). The present  
 253 study aimed to shed further light on the temporal relationships between QoL and levels of anxiety,  
 254 depression and negative symptoms as these have been demonstrated to be amenable to change  
 255 through the IC treatment (8,14,32).

### 256 4.1. Key findings

257 The cross-lagged panel model showed that prior levels of symptom severity and impairment in QoL  
 258 predict subsequent levels at the following assessment-point. Notably, stability among constructs was  
 259 highest for negative symptoms and QoL between 6- and 12-months follow-up. Despite the relative  
 260 stability of each construct over time, significant changes in variable levels could be shown between

261 baseline and 6-months follow up, whereas there was no significant change between 6- and 12-months  
262 follow up. This could be due to a certain generalization or ceiling effect of the intervention.

263 Three main indirect pathways leading to improvements after 12 months were detected. First, higher  
264 levels of QoL at baseline led to fewer negative symptoms after six months which even yielded further  
265 improvements in QoL after 12 months. Secondly, this points to a mediating effect of negative symp-  
266 toms on QoL over the course of a year. This mediating effect of negative symptoms on future QoL has  
267 not previously been recognized. This finding supports recent results based on the usage of change-  
268 scores that improvements in negative symptoms may be a relevant mechanism of change of ACT treat-  
269 ment (12). This implies that in order to optimize effects of ACT on QoL, severity of negative symptoms  
270 should be reduced during the early phases of the intervention. Such interventions then allow improv-  
271 ing QoL more than what would be expected, if the effect would be limited to the reduction of clinical  
272 symptoms.

273 High levels of negative symptoms tend to impair the social relations and general ability to participate  
274 in everyday life (33,34) which in turn causes a lower level of perceived QoL (35). This could explain the  
275 central role of negative symptoms as a mediating factor as shown by our model analysis.

276 In a third pathway, the reduction of depression after 12 months was achieved by improvements in  
277 negative symptoms after six months which in turn was determined by the level of QoL at baseline.  
278 However, this indirect effect is small and only reached a trend level. Notably, depression at 12-month  
279 follow up was also predicted by a small indirect effect through improvements of QoL from baseline to  
280 6-month follow-up. Interestingly, anxiety showed no association with other variables, although it sig-  
281 nificantly improved over time. This is in contradiction to previous results (e.g. Schmidt et al., 2018) but  
282 is in line with current guidelines suggesting that targeting depression and negative symptoms together  
283 may produce beneficial effects (36).

284 *4.2. Limitations*

285 While our study has several strengths (e.g. large sample size, patient sample that is hard to be treated,  
286 long follow-up), several limitations need to be mentioned. All variables were measured by only one  
287 indicator. This made it necessary to use manifest instead of latent variables, which may have underes-  
288 timated the path coefficients and the amount of explained variance in each dependent variable. Re-  
289 latedly, we assessed depression and anxiety by only one single item and together with negative symp-  
290 toms from the same instrument, which may have overestimated the correlations between them. In  
291 future studies, it is therefore recommended to assess these constructs by several assessments and  
292 different informants (e.g. clinician-ratings and self-reports). Another limitation refers to the fact that  
293 we could use only three assessment-points covering one year. It might be interesting in future studies  
294 to use more assessment-points and over a longer time-period to better capture the dynamic nature  
295 between severity of symptoms and QoL. Moreover, other factors that have not been included into the  
296 model (e.g. level of functioning, social support) to diminish model complexity may also have an im-  
297 portant impact on the assessed model variables (12).

#### 298 *4.3. Clinical implications*

299 Quality of life, negative and depressive symptoms showed a reciprocal interaction during the course  
300 of treatment. Anxiety symptoms, on the other hand, seem to be less influenced by this interaction. It  
301 could be interpreted that anxiety symptoms are a part of the psychosis itself and are present continu-  
302 ously, seemingly without affecting QoL in a significant way so that treatments specifically targeting  
303 anxiety are necessary.

304 Each construct is quite stable over time, in particular between 6 and 12 months, with small to medium  
305 effect sizes. One possible explanation for the strong association between 6 and 12 months may be  
306 might be that it is due to a generalization effect of the intervention where the improvement from the  
307 intervention reaches a plateau at which the effect stabilizes (37). Further, QoL and negative symptoms  
308 tend to have a more stable course than anxiety and depression, which fluctuate on a daily or weekly  
309 basis (38,39). This is well in line with the result that improvements mainly took place between T0-T1.

310 We detected three main pathways to improvements after 12 months that are only partially in line with  
311 previous literature: Level of QoL baseline leads to improvements in negative symptoms after 6 months  
312 which predicts larger improvements of quality of life after 12 months (=mediation effect). This implies  
313 clinically that one of the most efficient ways to improve QoL might be to target it directly but also to  
314 target negative symptoms as it has been done in ACT. Therefore, negative symptoms may be an im-  
315 portant mechanism of change of ACT. This is well in line with our previous studies (11,12,19).

316 Improvements in QoL after 6 months predict improvements in depression after 12 months via im-  
317 provements in negative symptoms. However, the indirect effect is small and only significant on a trend-  
318 level. It means that QoL at baseline determines the severity of negative symptoms after 6 months.  
319 Such improvements in negative symptoms may lead to improvements in depression as patients do not  
320 need to adopt negative symptoms as a dysfunctional coping strategy any longer to protect themselves  
321 from negative feedback from the social environment (12,14,19). This sequence of variables (negative  
322 symptoms and depression) is in line with our previous paper, but notably, depression had no effect on  
323 QoL (40–42).

#### 324 **Summary**

325 Since QoL, negative symptoms, and depressive symptoms influence each other, they should each be  
326 the target of therapeutic interventions. With regard to QoL, these are, in addition to the improvement  
327 of psychopathology, above all the social, personal, family, and occupational functioning level. Psycho-  
328 pathology has a major impact on the level of social functioning and is also associated with depression.  
329 Depression, in turn, negatively influences QoL.

330 Amongst the factors contributing to the reduction in negative and depressive symptoms during AC-  
331 CESS-treatment the fact, that continuous psycho- and pharmacotherapy are ensured from early on  
332 plays an important role, as well as the active follow up that the multi-professional team provides in  
333 situations of non-compliance, adverse life conditions or missed appointments. The intense and com-  
334 prehensive care that is provided for different medical and social needs, with the 24/7 possibility of

335 contact while the patients' everyday life can go on as an out-patient creates an environment, where  
336 negative and depressive symptoms are reduced, which in turn contributes to the improvement of QoL.  
337 Taken together, our results suggest that, in particular, negative symptoms may function as a potential  
338 mechanism of change of integrated care in patients with severe mental illness. Negative symptoms  
339 might be a major driver of non-adherence to therapy, which is one of the most important factors in  
340 continued psychopathology and its sequelae, such as decreased social and overall functioning, de-  
341 creased QoL and increased depression. Therefore, in addition to targeting QoL, negative symptoms,  
342 anxiety and depression directly, it seems especially promising to integrate interventions for QoL and  
343 negative symptoms to achieve better generalization effects on QoL and depression. Our results further  
344 propose that the ACT therapists could begin with the treatment of negative symptoms and QoL, which  
345 may then trigger or at least facilitate improvements in depressive symptoms and QoL after 12 months.

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#### 348 **CRedit authorship contribution statement**

349 Romy Schröter, Stefanie Schmidt and Martin Lambert designed the study. Romy Schröter wrote the  
350 protocol. Romy Schröter managed the literature searches and analyses. Stefanie Schmidt undertook  
351 the statistical analysis. Romy Schröter, Martin Lambert and Stefanie Schmidt drafted the manuscript.  
352 Romy Schröter, Stefanie Schmidt, Martin Lambert, Anja Rohenkohl, Anne Karow, Vivien Kraft, Frieder-  
353 ick Rühl, Daniel Luedecke and Jürgen Gallinat revised the manuscript. All authors are or were members  
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358 tors.

#### 359 **Conflicts of interest regarding the present research project**

360 Romy Schröter, Martin Lambert, Anja Rohenkohl, Vivien Kraft, Friederike Rühl, Daniel Lüdecke, Jürgen  
361 Gallinat, Anne Karow and Stefanie Schmidt declare none

362 **Conflicts of interest in general**

363 Romy Schröter: Nothing to declare

364 Martin Lambert: Consultant or speaker fees AstraZeneca, Bristol-Myers Squibb, Lilly Deutschland

365 GmbH, Janssen Cilag GmbH, Lundbeck GmbH, Otsuka Pharma GmbH, Roche Deutschland Holding

366 GmbH, Sanofi Aventis, Trommsdorff GmbH & Co. KG

367 Anja Rohenkohl: Has received speakers fee from Pfizer Pharma GmbH

368 Vivien Kraft: Nothing to declare

369 Daniel Luedecke: Speaker fees from Lundbeck GmbH

370 Friederike Rühl: Nothing to declare

371 Jürgen Gallinat: Speaker fees from Lundbeck GmbH, Otsuka Pharma GmbH, Janssen Cilag GmbH

372 Anne Karow: Consultant or speaker fees from AstraZeneca, Bristol-Myers Squibb, Lilly Deutschland

373 GmbH, Janssen Cilag GmbH, Lundbeck GmbH, Otsuka Pharma GmbH, Roche Deutschland Holding

374 GmbH

375 Stefanie Schmidt: Nothing to declare

376 **Data availability**

377 The datasets used and/or analysed during the current study are available from the corresponding au-

378 thor on reasonable request.

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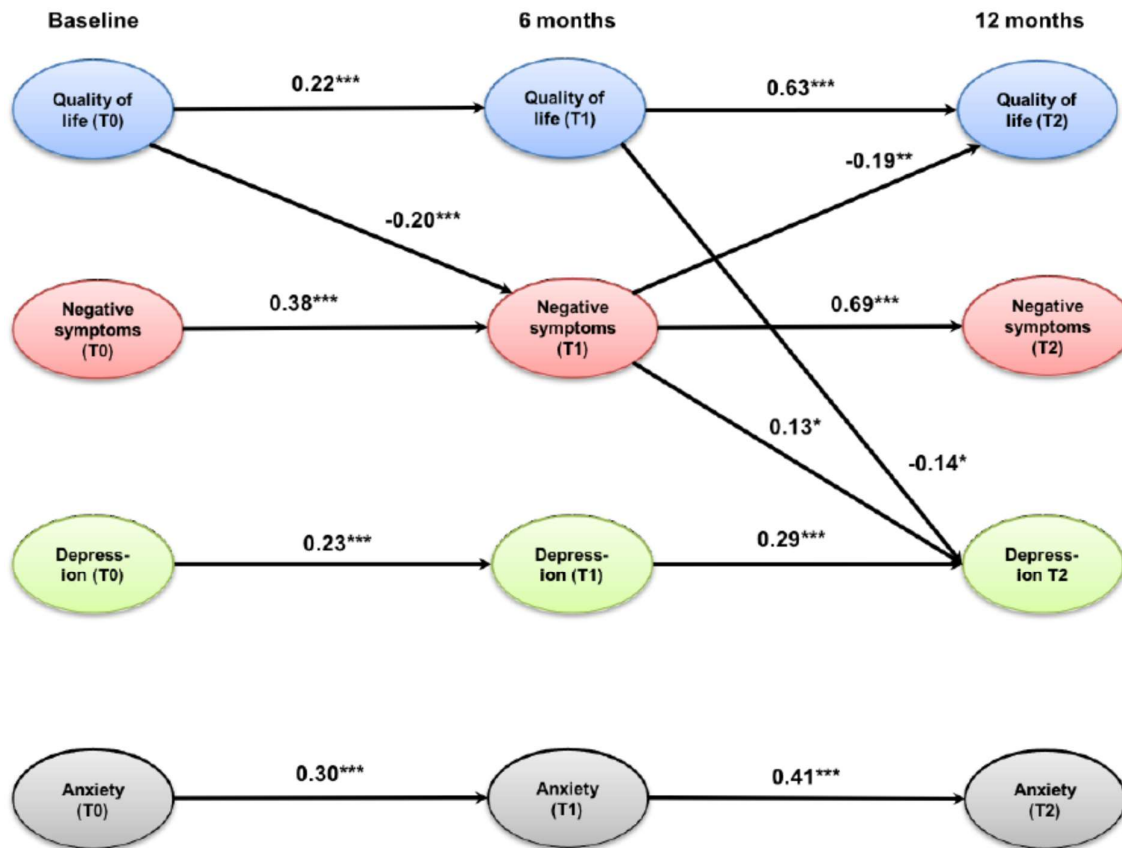
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518 **Caption for Fig.1**

519 **Figure 1.** Cross-lagged panel model of the relationships between quality of life, negative symptoms (self-neglect, blunted  
 520 affect, emotional withdrawal, motor retardation), depression, and anxiety Note. Only significant coefficients are displayed;  
 521 values are standardized path coefficients.  
 522 \*\*\* $p < .001$ , \*\*  $p < .01$ , \*  $p < .05$   
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526 **Tables and figures**527 **Table 1.** Demographic and psychopathological characteristics of the sample at baseline (T0)

	<b>N (%)</b>	<b>Mean</b>	<b>SD</b>
<b>Patient characteristics</b>			
Age	418	36.17	14.03
<i>Gender</i>			
Male	200 (47.8%)	-	-
Female	218 (52.2%)	-	-
<b>Diagnosis and phase of illness</b>			
<i>Diagnosis</i>			
Affective psychosis	125 (29.9%)	-	-
Non-affective psychosis	293 (70.1%)	-	-
<i>Diagnostic distribution</i>			
Schizophrenia	252 (60.3%)	-	-
Bipolar I disorder	62 (14.8%)	-	-
Schizoaffective disorder	57 (13.6%)	-	-
Others	47 (11.3 %)	-	-
<i>Phase of illness</i>			
First episode	115 (27.5%)	-	-
Multiple episode	303 (72.5%)	-	-
<b>Severity of illness</b>			
CGI-S total	398 (95 %)	5.53	.93
CGI-S depression	398 (95 %)	4.24	1.28
CGI-S cognitive	398 (95 %)	4.22	1.31
CGI-S positive	398 (95 %)	4.82	1.64
CGI-S negative	398 (95 %)	4.11	1.44
<b>Psychopathology</b>			
BPRS	418 (100 %)	78.47	20.78
<b>Functioning level</b>			
GAF	397 (95%)	39.51	12.48
<b>Quality of life, Q-LES-Q-18</b>			
QoL total score	382 (91%)	36.98	17.99
Subscore physical health	383 (92%)	34.92	19.23
Subscore subjective feelings	382 (91%)	39.66	21.87
Subscore leisure time activities	381 (91%)	34.26	23.44
Subscore social relations	382 (91%)	36.33	19.65

528 BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; Q-LES-Q18 Scores are transformed from 0-100.

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530

531 **Table 2.** Means, standard deviations and changes over time in BPRS and Q-LES-Q-18

	<b>T0</b> <b>M (SD)</b>	<b>T1</b> <b>M (SD)</b>	<b>T2</b> <b>M (SD)</b>	<b>T0-T1</b> <b>M (SD)</b>	<b>t</b> <b>(T0-T1)</b>	<b>p</b> <b>(T0-T1)</b>	<b>Cohens d</b> <b>(T0-T1)</b>	<b>T1-T2</b> <b>M (SD)</b>	<b>t</b> <b>(T1-T2)</b>	<b>p</b> <b>(T1-T2)</b>	<b>Cohens d</b> <b>(T1-T2)</b>
<b>BPRS total score</b>	78.47 (20.78)	50.18 (12.9)	49.38 (13.54)	28.30 (20.85)	25.357	<.001	1.36	0.64 (10.48)	1.064	0.288	0.061
BPRS 2 anxiety	4.67 (1.5)	2.95 (1.19)	2.96 (1.16)	1.78 (1.60)	21.134	<.001	1.11	0.01 (1.19)	0.14	0.889	0.008
BPRS 3 depression	4.02 (1.63)	2.97 (1.05)	2.97 (1.17)	1.05 (1.66)	12.009	<.001	0.63	-0.01 (1.21)	-0.184	0.854	-0.01
BPRS 13 self-neglect	3.22 (1.82)	2.23 (1.23)	2.22 (1.3)	1.02 (1.69)	11.441	<.001	0.60	0 (0.9)	0.062	0.950	0.003
BPRS 16 blunted affect	3.65 (1.7)	2.95 (1.17)	2.92 (1.25)	0.68 (1.73)	7.478	<.001	0.39	0.06 (1.09)	1.023	0.307	0.057
BPRS 17 emotional withdrawal	4.16 (1.75)	3.14 (1.43)	3.20 (1.36)	0.99 (1.88)	9.987	<.001	0.53	-0.04 (1.15)	-0.63	0.529	0.035
BPRS 18 motor retardation	2.83 (1.72)	1.92 (1.12)	1.85 (1.12)	0.91 (1.72)	9.947	<.001	0.53	0.08 (0.98)	1.429	0.154	0.08
<b>Q-LES-Q-18 total score</b>	2.48 (0.72)	3.23 (0.61)	3.30 (0.68)	-0.75 (0.80)	-20.121	<.001	-1.11	0.05 (0.59)	1.321	0.188	0.076

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535 **Table 3.** Bivariate correlations between model variables

Model variables	Assessment timepoints											
	1	2	3	4	5	6	7	8	9	10	11	
1 Negative symptoms T0	-											
2 Negative symptoms T1	.36***	-										
3 Negative symptoms T2	.35***	.69***	-									
4 Depression T0	.42***	.16**	.18**	-								
5 Depression T1	.15**	.48***	.28***	.28***	-							
6 Depression T2	.18**	.34***	.52***	.25***	.40***	-						
7 Anxiety T0	.11*	.03	-.06	.26***	.14**	-.01	-					
8 Anxiety T1	.11	.33***	.21***	.16**	.44***	.25***	.30***	-				
9 Anxiety T2	.12*	.28***	.40***	.16**	.26***	.57**	.15**	.48***	-			
10 QoL T0	-.17**	-.27***	-.24***	-.17**	-.10	-.15*	-.14**	-.04	-.10	-		
11 QoL T1	-.16**	-.38***	-.32***	-.17**	-.46***	-.31***	-.11*	-.38***	-.29***	.25***	-	
12 QoL T2	-.16**	-.37***	-.51***	-.14*	-.26***	-.59***	.04	-.24***	-.52***	.26***	.59***	

**Note.** Table shows correlation coefficients assessed at baseline (T0), after 6 months (T1) and after 12 months (T2).

*\*p<0.05, \*\*p<.01, \*\*\*p<.001*

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