



Longitudinal evidence for a relation between depressive symptoms and quality of life in schizophrenia using structural equation modeling

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ABSTRACT

Patients diagnosed with schizophrenia often report a low quality of life (QoL). The purpose of this study was to investigate whether we could replicate a cross-sectional model by Alessandrini et al. (2016, $n = 271$) and whether this model predicts QoL later in life. This model showed strong associations between schizophrenia spectrum symptoms and depressive symptoms on QoL, but lacked follow-up assessment. This model was adapted in the current study and the robustness was investigated by using a longitudinal design in which the association between baseline variables (including IQ, depression, schizophrenia spectrum symptoms as well as social functioning) and QoL during 3-years of follow-up was investigated. We included patients with a non-affective psychotic disorder ($n = 744$) from a prospective naturalistic cohort-study. In the cross-sectional model, with good measure of fit, both depression as well as social functioning was associated with QoL (direct path coefficient -0.28 and 0.41 , respectively). Additionally, the severity of schizophrenia spectrum symptoms was highly associated with social functioning (direct path coefficient -0.70). Importantly, the longitudinal model showed good measures of fit, which strengthens the validity of the initial model and highlights that depression prospectively affect QoL while schizophrenia spectrum symptoms prospectively influence QoL via social functioning. The negative, longitudinal impact of a depression on QoL highlights the need to focus on treatment of this co-morbidity.

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1. Introduction

The World Health Organization (WHO) defines quality of life (QoL) as “individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (Saxena et al., 1997). Despite debate regarding the precise definition of QoL (Awad and Voruganti, 2012; Post, 2014), guidelines label it as presumably one of the most important outcome measures in the long-term treatment of patients diagnosed with schizophrenia (National Institute for Health and Care Excellence, 2014).

Schizophrenia patients report a substantially lower QoL compared to healthy controls or their non-affected siblings (Kurs et al., 2005; Maat et al., 2012; Ritsner et al., 2000). By identifying factors that influence QoL in schizophrenia, specific treatment interventions could be used to improve low QoL. Several studies investigated the association between clinical variables and QoL in patients with schizophrenia (Conley et al., 2007; Górná et al., 2008; Priebe et al., 2011; Reine et al., 2003; Renwick et al., 2012) including a meta-analysis (Eack and Newhill, 2007). For example, the severity of psychotic symptoms is known to be negatively associated with QoL (Browne et al., 2000; Eack and Newhill, 2007; Górná et al., 2008) as well as the level of social functioning (Haro et al., 2014). Moreover, several studies consistently showed that QoL in schizophrenia patients is negatively associated with depressive symptoms (Reine et al., 2003; Renwick et al., 2012), which was also confirmed in a longitudinal study (Conley et al., 2007). This is important given the high prevalence of comorbid depressive symptoms in patients with schizophrenia (a median rate of 25%) (Buckley et al., 2009; Siris, 2000) and several options exist to treat comorbid depressive symptoms or depressive episodes in patients diagnosed with schizophrenia (e.g., optimizing antipsychotic dosages, switching to specific antipsychotics, motivating for physical exercise, addition of anti-depressant medication or cognitive behavioral therapy; van Rooijen et al., 2017).

It is not surprising that, in general, patients with depressive symptoms or episodes report worse QoL. Although overemphasizing current problems and underestimating the chances of recovery is often part of the depressive illness, feelings of sadness have a direct effect on wellbeing and satisfaction, cognitions about oneself, others and the future, which reinforce each other. Given the complexity of the construct QoL, it is presumable that other clinical variables may influence QoL as well. For example, depressive symptoms may influence social functioning and through this pathway influence QoL or they may have a direct effect on QoL. Former studies used mixed – effects regression analysis or analysis of variance to investigate the association between different variables influencing QoL (Conley et al., 2007; Reine et al., 2003; Renwick et al., 2012). Here we use structural equation modeling (SEM) that offers advantages since it is possible to perform longitudinal analyses and to include latent constructs. Moreover, SEM makes it feasible to assign an order by which the included variables affect each other and to what extent (Kline, 2005). For example, Alessandrini et al. (2016) used SEM and showed that “psychotic symptoms” (including positive, negative and general psychopathology symptoms) and neurocognition were directly associated with functioning, however, no direct association existed between psychotic symptoms and QoL nor between neurocognition and QoL (Fig. 1).

In this SEM-study by Alessandrini et al. (2016) the associations between psychotic symptoms, depression, neurocognition and functioning as determinants of QoL, were investigated in a cross-sectional study including 271 patients with schizophrenia. Their model underlined that depression was the most important determinant that was negatively associated with QoL, while functioning was directly positively associated with QoL. Based on these results, Alessandrini and colleagues suggested to focus on depressive symptomatology in the treatment of patients with schizophrenia as well as to improve skills involved in functioning (by interventions such as cognitive behavioral

therapy), since both depressive symptoms and functioning were important determinants of QoL. However, the findings of Alessandrini and colleagues are probably not generalizable to all schizophrenia patients because they included a relatively small group of patients with a long illness duration. Besides, they studied these patients only cross-sectionally and thereby were not able to address long-term outcomes. Confirmation with a longitudinal assessment is desirable because this strengthens the validity of the original model of Alessandrini and colleagues. Additionally, replication of the initial model in a longitudinal assessment will prove the stability between the different variables over time and thereby enables to formulate hypotheses concerning causal relations when investigating effects of interventions.

Taken together, previous studies show that there are several variables influencing QoL in schizophrenia patients but it remains unclear how these variables relate to each other and QoL. The identification of determinants of QoL is of clinical relevance, since they may guide treatment interventions. Therefore, the aim of the current study is to assess (i) whether the proposed cross-sectional model concerning determinants of QoL by Alessandrini and colleagues is supported by findings from a more diverse and larger group of patients and (ii) whether this model also determines QoL in a longitudinal perspective, in which the association between baseline variables and QoL at three-years of follow-up will be investigated.

2. Methods

2.1. Subjects

The data for this study was derived from the multicenter study ‘Genetic Risk and Outcome in Psychosis’ (GROUP) as described earlier (Korver-Nieberg et al., 2012). The GROUP study was a longitudinal cohort study that recruited patients ($n = 1119$) diagnosed with a non-affective psychotic disorder based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM IV; American Psychiatric Association, 2000). As the vast majority (90%) of patients was diagnosed with a schizophrenia-spectrum disorder, we will refer to ‘schizophrenia-spectrum disorder’ throughout the manuscript (Korver-Nieberg et al., 2012). The GROUP study consisted of three measurements (i.e., baseline (T0), three- (T1) and six-year (T2) follow-up). In the present study, we used data from T1 and T2, since the *Calgary Depression Rating Scale for Schizophrenia* (CDSS) was applied at these time points. For the cross-sectional analyses, we included patients with QoL data at T1 ($n = 744$). For the longitudinal analyses, we included patients for whom QoL data on both T1 and T2 were available ($n = 544$).

2.2. Measures

2.2.1. Quality of life

For assessing QoL, we used the *World Health Organization QoL Scale Brief Version* (WHOQOL-BREF; The WhoQOL Group, 1998). This self-reporting questionnaire includes 26 items comprising four domain scores (i.e., physical health (7 items), psychological health (6 items), social relationships (3 items) and environmental health (8 items)) and two general items measuring individual's overall QoL and health satisfaction. All items are rated on a 5-point Likert-scale, resulting in a mean domain score, in which higher scores reflect better QoL in the concerning domain. Of note, the four original domain sum scores were used in the analyses (following Heering et al., 2015). The QoL has shown robust validity in an adult psychiatric population in the Netherlands (Trompenaars et al., 2005).

2.2.2. Functioning

Social functioning was assessed with the *Global Assessment of Functioning* (GAF) scale (American Psychiatric Association, 2000). We used the GAF as it is a widely used instrument and it gives a broad reflection of the degree of functioning in a social context, but also recreational.

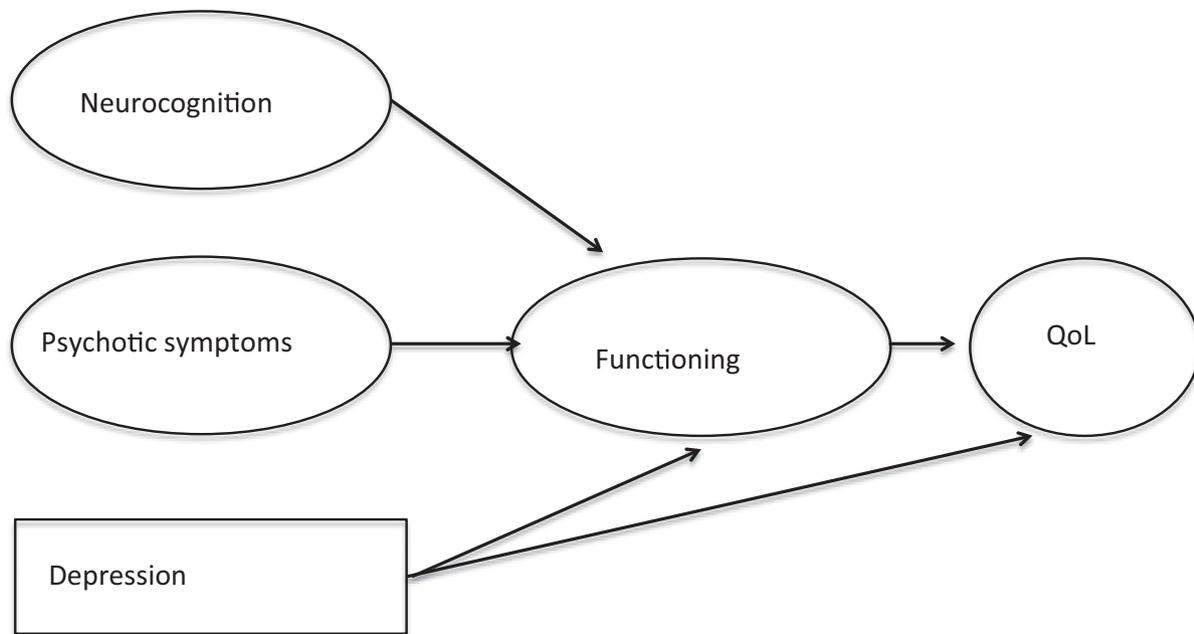


Fig. 1. Cross-sectional model proposed by Alessandrini et al. (2016). Cross-sectional model proposed by Alessandrini et al. (2016) – illustrating the effects of “psychotic symptoms” (i.e., positive, negative and general psychopathology as measured with the PANSS) symptoms, neurocognition, depressive symptoms and functioning on QoL. Ovals represent latent variables and rectangles represent observed variables. QoL = quality of life.

Throughout the manuscript we will refer to the GAF as ‘social functioning’. The GAF ranges from 0 to 100 and higher scores reflect better social functioning.

2.2.3. Clinical symptoms

To assess the severity of the depressive symptoms, the CDSS (Addington et al., 1990) was administered by trained investigators. The CDSS is a structured interview, designed to assess the severity of depressive symptoms in patients with schizophrenia (Lako et al., 2012). The CDSS consists of nine items, rated on a scale ranging from 0 (*absent*) to 3 (*severe*). Higher scores reflect more severe depressive symptoms and a score of 6 or higher is often used as cut-off point for a clinically relevant depressive episode (Sarró et al., 2004). In the present sample, the variance in depression scores was limited and consequently we dichotomized this variable based on a score of ≤ 5 or > 5 .

To measure the severity of positive, negative and general psychopathology symptoms the *Positive and Negative Syndrome Scale* (PANSS; Kay et al., 1987) was administered. The PANSS consists of 30 items, in which each item is scored on a scale ranging from 1 (*absent*) to 7 (*extreme*), measuring three domains: positive symptoms (e.g., delusions, disorganization and hallucinations), negative symptoms (e.g., social and emotional withdrawal) and general psychopathology (e.g., anxiety, poor attention and somatic concern), with higher scores reflecting more severe symptoms. Of note, PANSS total domain scores were used in the analyses (i.e., the PANSS total, referred to as ‘schizophrenia spectrum symptoms’, based on the positive, negative and general psychopathology subscales). Of note, Alessandrini et al. (2016) used psychotic symptoms to describe this latent variable, however, we consider the term ‘schizophrenia spectrum symptoms’ more appropriate.

In line with an earlier study performed in the same sample, we used a composite measure of IQ to assess neurocognition (Maat et al., 2012). This composite score consisted of Arithmetic (working memory), Digit Symbol-Coding (processing speed), Block Design (reasoning and problem solving) and Information subtests (verbal comprehension) of the *Wechsler Adult Intelligence Scale* (WAIS) III (Blyler et al., 2000; Wechsler, 1997). For the sake of clarity, we will refer ‘IQ’ instead of neurocognition throughout the manuscript. Additionally, in line with

earlier research identifying the important influence of ‘age’ and ‘gender’ on outcomes measures (Haddock et al., 2006; Röder-Wanner and Priebe, 1998), we also included both variables in our model.

2.3. Statistical analysis

For all the analyses release 5.0 of the GROUP database was used. Differences in demographic characteristics and illness severity between patients with both T1 and T2 data available and patients with T1 data only were investigated using χ^2 -tests or *t*-tests. For all the SEM analyses, we used M-plus (Muthén and Muthén, 1998). SEM is a robust statistical technique that enables to perform a multiple regression analysis. However, compared to other regression analysis techniques, important improvements of SEM are the fact that latent constructs are included (by which the influence of variance is reduced), a direction can be given in which order and to what extent variables are influencing each other (Kline, 2005).

First, following the earlier proposed model by Alessandrini et al. (2016), we investigated the influence of different clinical variables on QoL at T1 (Fig. 1). Second, we tested whether the proposed model also fitted the longitudinal data: by assessing whether QoL during follow-up (T2) was predicted by clinical variables (i.e., social functioning, clinical symptoms and IQ) three years earlier (T1). Based on previous findings (Haddock et al., 2006; Röder-Wanner and Priebe, 1998), we also investigated in both models whether age and gender influenced QoL.

The fit indices χ^2 , Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI) and Standardized Root Mean Square Residual (SRMR) were used to evaluate the fit of the models. The chi-square index is a badness-of-fit-index and should be non-significant ($p > 0.05$). RMSEA values smaller than 0.08 indicate that the fit of the model is sufficient and values smaller than 0.05 indicate a good fit. SRMR values smaller than 0.10 indicate a good fit of the model. Lastly, CFI values higher than 0.90 indicate a good fit (Kline, 2005). QoL and PANSS domain scores were modeled as two latent variables based on the proven validity of both questionnaires. In our SEM model, associations between variables are expressed as standardized regression coefficients (Cohen, 1988). Moreover, *p*-values smaller than 0.01 were regarded as statistically significant.

Our model was theoretically constructed based on the results of Alessandrini et al. (2016). In addition, we added some correlations to enhance the fit of the model, all based on modification indices provided by M-plus. The following correlations were added in our *cross-sectional* model: PANSS positive scale with the PANSS negative scale, PANSS total score with depression (i.e., the dichotomized depression score) and PANSS total score with IQ. With regard to our *longitudinal* model, we also added one novel correlation (i.e., between the QoL domains 'psychological health' and 'social relationships') while the correlation between PANSS total score with depression appeared to be redundant and was not used in the longitudinal model.

3. Results

3.1. Sample characteristics

Table 1 summarizes the sample characteristics and clinical variables at T1 and T2. The patients who completed follow-up assessment T2 showed a significantly higher level of social functioning, a lower severity of schizophrenia spectrum symptoms (with respect to negative and positive symptoms) and a more favorable QoL (however only with respect to environmental domain) at T1 compared to the patients who did not complete follow-up (Table 2). Patients with or without complete follow-up data did not differ significantly with respect to the severity of depressive symptoms, general symptoms as measured with the PANSS, IQ and had a more favorable QoL (with respect to physical, psychological and social domain) (Table 2).

3.2. Correlations

Pearson's correlations between QoL, IQ, social functioning and schizophrenia spectrum symptoms were calculated cross-sectionally (Supplementary Table S1) and longitudinally (i.e., QoL at T2 and clinical variables at T1; Table S2). In both cross-sectional and longitudinal analyses, the direction of the correlations was as expected, i.e., schizophrenia spectrum symptoms were negatively associated with IQ, social functioning and QoL. In both analyses IQ was not significantly associated with the psychological and social QoL domains, nor with positive symptoms in the longitudinal analyses.

Table 1
Baseline demographic characteristics of the total sample at T1 (n = 744).

	n ^a	Mean (SD)
Age, years	744	30.64 (7.23)
Gender, n (% male)	744	76.5
Age at psychosis onset, years	744	23.13 (6.60)
Use of antipsychotic medication, n (% yes)	627	542 (73)
T1		
QoL physical	743	3.63 (0.67)
QoL psychological	744	3.51 (0.65)
QoL social	742	3.34 (0.85)
QoL environmental	743	3.72 (0.61)
GAF	632	60.49 (15.71)
PANSS, positive	728	10.93 (4.47)
PANSS, negative	713	11.72 (5.09)
PANSS, general	718	23.90 (6.99)
CDSS	713	2.04 (2.88)
CDSS, % depressed (≥6)	713	13.3
IQ	568	98.64 (16.54)
T2		
QoL physical	544	3.65 (0.71)
QoL psychological	544	3.50 (0.66)
QoL social	544	3.35 (0.87)
QoL environmental	544	3.76 (0.63)

QoL = quality of life; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Symptom Scale; CDSS = Calgary Depression Rating Scale for Schizophrenia.

^a Of note, as the used questionnaires differed between participating centers we provide the number of patients of whom questionnaires were available.

3.3. SEM – model, cross-sectional

The structural equation model, based on the measures at T1 showed acceptable fit measures (Fig. 2): RMSEA = 0.07, CFI = 0.92 and SRMR = 0.06. Depression and QoL were significantly negatively associated (direct path coefficient -0.28), as were social functioning and QoL (direct path coefficient 0.41). Schizophrenia spectrum symptoms and social functioning were strongly negatively associated (direct path coefficient -0.70), but there were no direct links between depression and social functioning. Non-significant associations were observed between age or gender and QoL. For IQ, there was no direct link with social functioning in the model. As we considered IQ an important measure, we decided to include IQ in our model, but we found a non-significant association between IQ and QoL. Schizophrenia spectrum and depressive symptoms, IQ and social functioning explained 33% of the variance in QoL.

3.4. SEM – model, longitudinal

To investigate the pathways contributing to QoL at follow-up, we constructed a second SEM-model in which we substituted QoL at T1 for QoL at T2 and remained all clinical variables as assessed at T1 (Fig. 3). Again, this model showed acceptable fit measures (RMSEA = 0.08, CFI = 0.90 and SRMR = 0.08) and showed identical pathways as for the cross-sectional model. Although slightly less strong, depression and social functioning were both associated with QoL during follow-up (direct path coefficient -0.22 respectively 0.34). Likewise, schizophrenia spectrum symptoms and social functioning were strongly associated (direct path coefficient -0.69). Again, there were no direct links between depression and social functioning, nor between IQ and social functioning. Comparable with the cross-sectional model, we found a non-significant association between IQ and QoL. In the longitudinal model, schizophrenia spectrum and depressive symptoms, IQ and social functioning explained 21% of the variance in QoL. Finally, non-significant associations were found between age and QoL. In contrast to the cross-sectional model, gender was significantly associated with QoL during follow-up (gender direct path coefficient: 0.15, $p = 0.001$).

4. Discussion

In the current study, we aimed to replicate an earlier cross-sectional SEM-model by Alessandrini et al. (2016) in a prospective cohort study. The current study demonstrated that first, depression negatively affect QoL directly, second, social functioning is directly associated with QoL and third, schizophrenia spectrum symptoms prospectively influence QoL via an indirect pathway, which is via social functioning. By using SEM, which enables to investigate several variables concomitantly, this study reveals an adequate fit of both a cross-sectional and prospective model, applied to a large sample of patients diagnosed with a schizophrenia-spectrum disorder (n = 744).

An important feature of this study was that we could reproduce the relations in the model of Alessandrini and colleagues both in a longitudinal and cross-sectional design. Replication of initial results, in general, is difficult (Open Science Collaboration, 2015), but feasible for the initial model determined by Alessandrini et al. (2016). Moreover, our longitudinal assessment strengthens the validity of the initial model and emphasizes the association between variables included in this model.

Depression contributes to a lower QoL cross-sectionally and also contributes to a lower QoL three years later. As mentioned by Alessandrini and colleagues, the significance of depressive symptoms were earlier demonstrated by, among others, the study of Fervaha et al. (2015). The latter study compared the association between symptom domains and illness severity (which was rated by clinicians but also by patients). They showed that the strongest correlation between the patients-rated illness severity was with depressive symptoms, while the strongest correlation of the clinicians-rated illness severity was

Table 2
Differences in clinical variables at baseline of patients who completed T1 and T2 (n = 544) versus those who only completed T1 (n = 200).

	T1 + T2 (n = 544)		T1 only (n = 200)		p**
	n ^a	Mean (SD)	n ^a	Mean (SD)	
Age, years	544	30.74 (7.36)	200	30.35 (6.88)	0.51
Gender, n (% male)	544	410 (75)	200	159 (80)	0.24
Age of onset first psychosis, years	544	23.18 (6.74)	200	22.99 (6.22)	0.73
Use of antipsychotic medication, n (% yes)	460	396 (86)	167	146 (87)	0.67
Number of psychotic episode(s) since last assessment at T1	467	0.48 (0.50)	184	0.37 (0.49)	0.02
Hospitalisation during psychosis	464	0.38 (0.49)	189	0.46 (0.50)	0.066
QoL physical	543	3.64 (0.68)	200	3.60 (0.66)	0.42
QoL psychological	544	3.52 (0.66)	200	3.48 (0.61)	0.46
QoL social	542	3.37 (0.84)	200	3.31 (0.89)	0.44
QoL environmental	544	3.77 (0.61)	199	3.59 (0.61)	0.001
GAF	451	62.36 (14.80)	181	55.85 (16.94)	<0.001
PANSS, positive	536	10.62 (4.20)	192	11.78 (5.04)	0.005
PANSS, negative	525	11.33 (4.61)	188	12.82 (6.12)	0.003
PANSS, general	530	23.55 (6.84)	188	24.89 (7.30)	0.02
CDSS	524	2.00 (2.82)	189	2.14 (3.03)	0.13
CDSS, % depressed (≥6)	524	12	189	17	0.09
IQ	422	99.68 (16.25)	146	95.61 (17.1)	0.01

QoL = quality of life; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Symptom Scale; CDSS = Calgary Depression Rating Scale for Schizophrenia.

^a Of note, as the used questionnaires differed between participating centers we provide the number of patients of whom questionnaires were available.

** p-Values < 0.01 in bold.

found for positive symptoms. In sum, clinicians might concentrate on psychotic symptoms, while patients experience the most nuisances from depressive symptoms.

The negative impact of a depressive episode on QoL highlights the need to enhance treatment availabilities against this co-morbidity. Interventions against depressive symptoms and depressive episodes in patients with schizophrenia were recently reviewed by our group (van Rooijen et al., 2017). Unfortunately, treatment studies investigating depressive symptoms as primary outcome are sparse, the duration of these studies was often short and the majority focused on depressive symptoms (instead of depressive episodes), which hampers

generalization of results to distinct depressive episodes. Nevertheless, depression and depressive symptoms are treatable and the present study indicates the relevance of recommendations regarding the existing treatment options. Moreover, verified associations between depression and suicide, substance abuse and reduced treatment adherence (Baker et al., 2005; Conley et al., 2007; Karvonen et al., 2007; Schwartz and Cohen, 2001) should urge clinicians to treat a depressive episode.

Depression did not influence the level of social functioning. These results are slightly different from those of Alessandrini et al. (2016), who report a weak association (direct path coefficient -0.11 , $p = 0.026$).

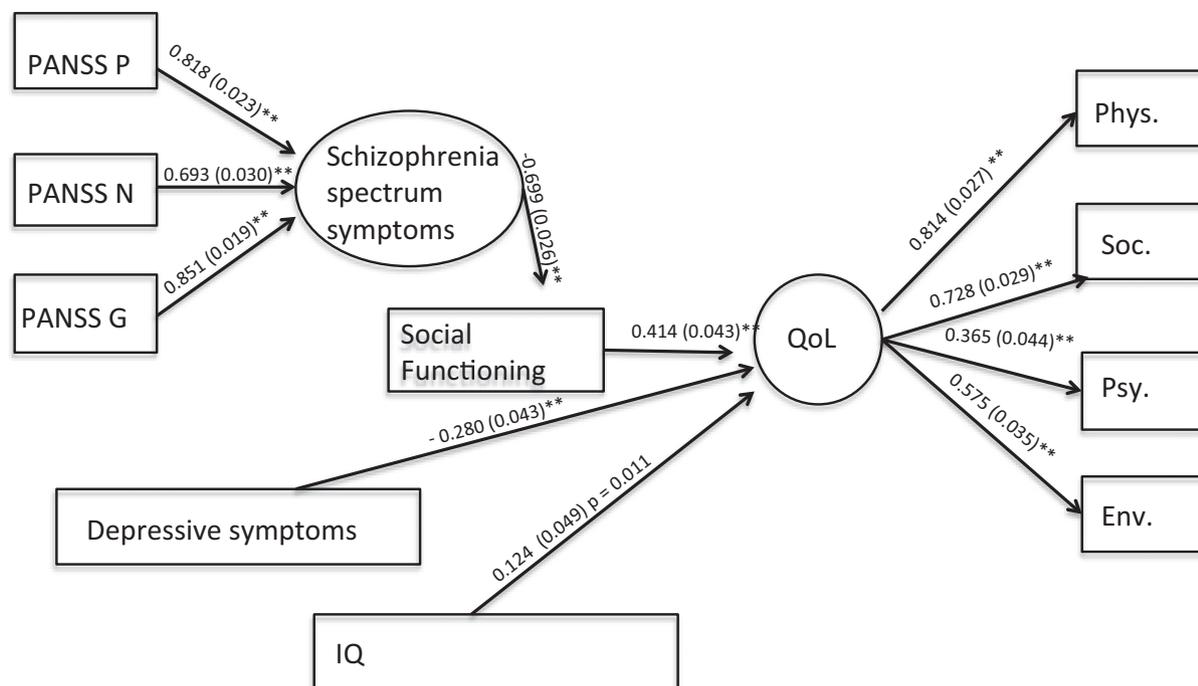


Fig. 2. Cross-sectional model at T1 (n = 744). Structural Equation Model (SEM) with IQ, social functioning, depressive and schizophrenia spectrum symptoms and quality of life at T1 (n = 744). Above the arrows the standardized parameter estimates, between the brackets the standard error. Ovals represent latent variables and rectangles depict observed variables. Schizophrenia spectrum symptoms and QoL were both modeled as latent variables. Fit indices: RMSEA = 0.07, CFI = 0.92 and SRMR = 0.06. CDSS = Calgary Depression Scale for Schizophrenia; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Symptom Scale; PANSS P = positive factor; PANSS N = negative factor; PANSS G = general psychopathology factor; QoL = quality of life; Env = environmental domain; Psy = psychological domain; Soc = social domain; Phys = physiological domain. Of note, although not included in the figure the model also included the variables age and gender. ** indicates $p < 0.001$.

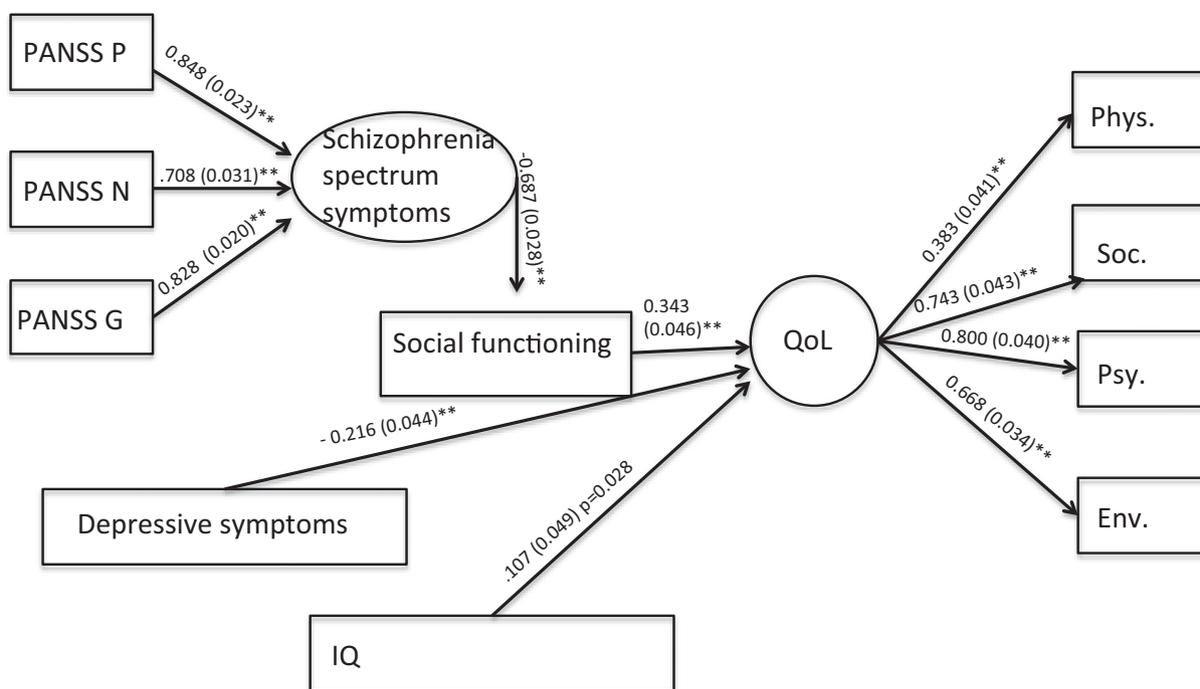


Fig. 3. Longitudinal SEM-model ($n = 544$). Structural equation model (SEM) with IQ, social functioning, depressive and schizophrenia spectrum symptoms and quality of life at T2 ($n = 544$). Fit indices: RMSEA = 0.08, CFI = 0.90 and SRMR = 0.08. Above the arrows the standardized parameter estimates, between the brackets the standard error. Ovals represent latent variables and rectangles depict observed variables. Schizophrenia spectrum symptoms and QoL were both modeled as latent variables. CDSS = Calgary Depression Scale for Schizophrenia; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Symptom Scale; PANSS P = positive factor; PANSS N = negative factor; PANSS G = general psychopathology factor; QoL = quality of life; Env = environmental domain; Psy = psychological domain; Soc = social domain; Phys = physiological domain. Of note, although not included in the figure the model also included the variables age and gender. ** indicates $p < 0.001$.

However, the use of different questionnaires to measure social functioning, the overall lower mean score of depression severity in our sample and the use of a dichotomized variable of depression score in our study might explain this difference. [Alessandrini et al. \(2016\)](#) referred to the findings of [Galderisi et al. \(2014\)](#) to explain the observed weak association between depression and social functioning. [Galderisi et al. \(2014\)](#) included 921 patients diagnosed with schizophrenia and used SEM to investigate the association between several variables (including illness related variables, context-related factors and personal resources) with real-life functioning (measured by a scale that included 'social, vocational, and everyday living outcomes'; [Galderisi et al., 2014](#)). They found no association between depression and real-life functioning, which was explained by the hypothesis that depression might negatively affect a 'person's self-evaluation of functioning', but does not lead to a worse real functioning ([Galderisi et al., 2014](#)).

Schizophrenia spectrum symptoms were strongly negatively associated with social functioning (direct path coefficient of -0.71) and social functioning was directly influencing QoL (direct path coefficient of 0.41). These results are comparable with those of [Alessandrini et al. \(2016\)](#), who showed a direct path coefficient of -0.7 between schizophrenia spectrum symptoms and functioning and of 0.26 between functioning and QoL. The first finding underscores the widely accepted notion that treating schizophrenia spectrum symptoms is needed to improve social functioning ([National Institute for Health and Care Excellence, 2014](#)). However, the latter finding underlines that improvement of social functioning is needed to eventually improve QoL. Indeed, social functioning covers a wide concept including the possibilities to have work, daytime activities and contact with others, which are all important factors in the long-term treatment of patients. Interestingly, several studies in this field focused on skills enhancing social cognition as an important determinant of social functioning ([Dodell-Feder et al., 2015](#); [Lysaker et al., 2015](#)). Social cognition is a broad concept, including different cognitive skills involved in social situations, among others, theory of mind and emotion perception. Also, an earlier study performed in

the GROUP sample showed that social cognition (and more specific 'theory of mind') was negatively associated with QoL ([Maat et al., 2012](#)), which underlines a noteworthy association between social cognition, social functioning and QoL.

Finally, [Alessandrini et al. \(2016\)](#) showed a weak association between neurocognition and functioning. However, in our model there was no association between IQ (as measurement of neurocognitive functioning) and social functioning. Although we included IQ in our model, we found non-significant associations between IQ and QoL. The fact that IQ has less influence on QoL, has been previously revealed by a meta-analysis showing non-significant or inverse associations between most neurocognitive measures and QoL ([Tolman and Kurtz, 2012](#)). Of note, the assessment of IQ in our study included only certain domains of neurocognitive functioning ([Nuechterlein et al., 2008](#)) which also might explain the difference between our study and that of [Alessandrini et al. \(2016\)](#). Furthermore, estimated IQ in the present patient sample was relatively high (mean: 98.64), even though the patient group scored approximately 1SD below the control group ([Korver-Nieberg et al., 2012](#)), this relatively high IQ suggests that we included a relatively high functioning group of patients which may also explain the lack of associations with QoL. Further SEM-models should elaborate on these results by also including other cognitive domains (e.g., visual learning) ([Nuechterlein et al., 2008](#)).

Many studies have investigated the associations between clinical variables and different definitions of QoL. There is an ongoing debate regarding the precise definition of QoL and which domains are part of the construct, and this is reflected by the wide use of different instruments to measure QoL ([Awad and Voruganti, 2012](#)).

Apart from our large dataset and our cross-sectional and longitudinal design, some limitations need to be taken into account. First, although we included multiple clinical variables, we are aware that there might be more determinants of QoL or social functioning (e.g., the use of medication, medication side effects including extrapyramidal side effects, insight, personality traits etc.), which especially

might influence longitudinal measures of QoL. The GROUP study used a naturalistic design. Consequently, patients were included with substantial variation in medication regimes (i.e., with respect to dosage, type and duration of treatment), other treatments (e.g., occupational therapy or cognitive behavioral therapy) and differences in treatment setting, which could not be adequately modeled. Second, patients who were lost to follow-up represent a subgroup with more severe psychopathology and, consequently, our longitudinal results are only applicable to a group of patients with relatively good social functioning. It therefore remains insufficiently clear whether the observed associations are generalizable to those with (initially) lower social functioning. Third, as mentioned earlier, we are aware that we did not include social cognition and only a few cognitive domains. Therefore, including other cognitive domains might have led to different findings. Fourth, we acknowledge that other associations between included variables are possible, besides those tested in the current model (e.g., IQ might be influenced by depression). We did not explore these associations in current study because our main purpose was to assess whether the proposed cross-sectional model by Alessandrini et al. (2016) was supported by findings from a different and larger sample. Fifth, we have attempted to replicate the Alessandrini et al. (2016) model as good as possible, however, due to the inclusion of different instruments, there are differences between the used variables in the two studies and it is not a completely overlapping replication study.

5. Conclusion

In this unique longitudinal study investigating depressive symptoms in patients with schizophrenia-spectrum disorder, we were able to retest an earlier constructed SEM model in a cross-sectional but also in a longitudinal design, hereby enhancing the validity of this model. SEM analyses enabled us to include several (latent) variables and to allocate an order in which clinical variables are associated with each other and QoL, and to what extent. In this study, depressive symptoms were associated with patients-rated QoL, highlighting the need to target treatment of depressive symptoms. Moreover, social functioning had a direct influence on QoL, while schizophrenia spectrum symptoms were indirectly, via social functioning, associated with QoL.

Conflict of interest

None to declare.

Contributors

Geeske van Rooijen (GvR) and Arija Maat (AM) managed the literature search, which formed the basis of current study. GvR and Maaike van Rooijen (MvR) performed the SEM - analysis. The first draft of the manuscript was written by GvR, MvR, AM, Carin Meijer, Jentien M. Vermeulen, Henricus G. Ruhé, Lieuwe de Haan reviewed the manuscript more than once. All authors, including the GROUP investigators, agreed to the manuscript in its current form.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2019.04.011>.

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