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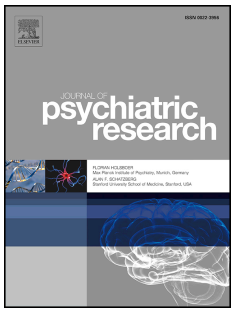

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Proposing a Causal Pathway for Health-Related Quality of Life in People with Psychotic Disorders

Running title: Predictors of HRQoL and Role of Global Functioning

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Abstract

This study aimed to establish independent predictors for health-related quality of life (HRQoL) in people with psychotic disorders, and the mediating role of global functioning in those relationships. Data for 1,642 people collected as part of the second Australian National Survey of Psychosis were analyzed. The Assessment of Quality of Life (AQoL)-4D and the Personal and Social Performance scale were used for assessing HRQoL and global functioning respectively. The study commenced with a theoretical model comprised of 26 sociodemographic and clinical variables. A predictive model for HRQoL was built up using a purposeful selection strategy to arrive at a set of clinically meaningful, independent predictors. The mediating effect of global functioning was then assessed. Seven variables were found to have an independent effect on HRQoL: perception of loneliness, number of negative symptoms, use of psychotropic and anticholinergic medications, course of disorder, lifetime histories of chronic pain and cardiovascular disease and living arrangements at the time of the interview. All variables except perceived loneliness and chronic pain were partially mediated through global functioning. This final model explained 46% of the variance in HRQoL, with loneliness and number of negative symptoms the strongest predictors. Evidence in support of a credible causal pathway for HRQoL in people with psychotic disorders, mediated by global functioning was presented. The importance of the quality of social relationships was highlighted, and potential targets for improving the HRQoL of this population identified.

Keywords: quality of life; psychotic disorders; models, theoretical; loneliness

1. Introduction

The quality of life (QoL) of people with psychotic disorders has been recognized as an important outcome for this population (Oliver et al., 1997a; 1997b). QoL has been defined by the World Health Organization (1997) as "an individual's 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". QoL is thus a construct that includes both objective and subjective components, and both can involve "physical, psychological, interpersonal, spiritual, financial, political, temporal, and philosophical dimensions" (Fayers and Machin, 2016).

Achieving better QoL or health-related quality of life (HRQoL) (i.e., aspects of QoL impacted by a disease and/or its treatment (Fayers and Machin, 2016)), is of increasing interest to both clinicians and policy makers. However, there is little information about the causal pathway to achieving QoL/HRQoL in people living with psychosis, information that would enable the development of strategies targeted at improving the QoL of people with psychotic disorders and, in turn, the QoL of their relatives and/or carers.

Another important outcome for people with psychotic disorders is their global functioning. Functioning is concerned with the person's ability to perform their roles and participate in life (Bowling, 2005). Impairments in functioning are common in people with psychosis and global functioning is associated with their QoL/HRQoL (Nevarez-Flores et al., 2019). Given the nature of global functioning and QoL/HRQoL, it is anticipated that global functioning will lie on the QoL and HRQoL causal pathways in this population. This position is consistent with global functioning mediating the effects of psychotic symptoms and neurocognitive impairment, and to a lesser extent the effects of depression on the HRQoL of people with schizophrenia (Alessandrini et al., 2016). This position is also consistent with community/social functioning mediating the effects of positive and negative symptoms,

cognitive abilities and employment status on the QoL of this population (Chan and Yeung, 2008). Global functioning has also been identified as a predictor for both objective and subjective QoL (Kusel et al., 2007), assessed with the Quality of Life Scale and Manchester Short Assessment of Quality of Life respectively. Similarly other predictors for objective and subjective QoL have been identified as including depressive symptoms (Kusel et al., 2007; Suttajit and Pilakanta, 2015), negative symptoms (Aki et al., 2008; Kusel et al., 2007; Tomotake et al., 2006; Yamauchi et al., 2008), cognitive deficits (Cruz et al., 2016; Kurtz et al., 2012), social contact and personal relationships (Kusel et al., 2007). Predictors of HRQoL in people with psychotic disorders also include global functioning (Alessandrini et al., 2016) and depressive symptoms (Chou et al., 2014; Stubbs et al., 2015). An extensive list of predictors of QoL and HRQoL, classified on the basis of the instruments used for their assessments is presented in Fig. 1.

Please insert Figure 1 around here.

With reference to the psychiatric literature above and our previous research (Neil et al., 2018; Nevarez-Flores et al., 2020; 2019), we in turn propose a credible causal model for HRQoL for people with psychotic disorders based on the mediating effect of global functioning and a suite of putative sociodemographic and clinical variables (Fig. 2).

Please insert Figure 2 around here.

With reference to the theoretical causal model for HRQoL in people with psychotic disorders, this study aimed to establish a statistical model of HRQoL mediated by global functioning. We hypothesized that 1) global functioning will be a strong predictor of HRQoL, 2) independent predictors of HRQoL will include severity of symptoms (particularly depressive and negative symptoms) and social experiences (such as social dysfunction and perception of loneliness) and, 3) adding global functioning to a model including these

predictors will attenuate some but not all of the effects for some predictors, supporting a causal model of partial mediation through global functioning.

2. Material and Methods

This study analyzed data collected from participants of the 2010 Australian National Survey of Psychosis, the Survey of High Impact Psychosis (SHIP) (Morgan et al., 2012) who screened positive for psychosis and met the International Classification of Diseases 10th revision (ICD-10) criteria for a psychotic disorder. The survey was undertaken at seven sites in five Australian states, and covered about 10% of the Australian population aged 18-64 years. The survey methodology employed a two-phase design. In Phase 1, undertaken in March 2010, public specialized mental health services (inpatient, outpatient, ambulatory and community mental health services) and non-government organizations (NGOs) supporting people with mental disorders screened all individuals, to identify those likely to meet diagnostic criteria for psychosis. Public specialized mental health service administrative records covering the 11-months prior to the survey month were also screened. In Phase 2, undertaken from April 2010 to March 2011, people who screened positive for psychosis in Phase 1 (1,825 of 7,955 participants) were randomly selected for interview; 1,642 met the ICD-10 criteria for a psychotic disorder. Information was collected on 32 modules during the interview, including: sociodemographic characteristics, symptomatology, substance use and physical conditions, medication use, service utilization, community sector support, overall functioning and HRQoL. The interviews were undertaken by trained interviewers who were also mental health professionals.

Full methodological details are provided elsewhere (Morgan et al., 2014; 2012). Variables included in this study were chosen with reference to the theoretical causal model of HRQoL (Fig. 2).

2.1. Measures

Health-related quality of life. HRQoL was assessed with the Assessment of Quality of Life (AQoL)-4D (Hawthorne et al., 1999), a generic instrument comprised of four dimensions: independent living, social relationships, mental health and senses, each of which consists of three items assessed over the last 7-days. The AQoL-4D can provide a score for each item and dimension and be used as a preference-based measure of HRQoL through assessment of the health state "utility value". Utility values range from -0.04 (worse than death) to 1.0 (full health), with 0.0 equating to death. Previous work has shown that the AQoL-4D can validly (Herrman et al., 2002) and sensitively assess HRQoL in this population (Neil et al., 2018), and distinguish between functioning and social experiences (Nevarez-Flores et al., 2020). The instrument was administered by an interviewer, and rated by the participant.

Global functioning. Global functioning was assessed through an interviewer rated assessment employing the Personal and Social Performance scale (PSP) (Morosini et al., 2000), a 100-point single-item rating scale subdivided into 10-intervals. The PSP assesses functioning within four domains: socially useful activities, personal and social relationships, self-care and disturbing and aggressive behaviours based on participant's responses and clinical judgment.

Social experiences in the last 12-months. Social dysfunction was assessed through an interviewer-rated assessment of participants' social dysfunction including social drive (no dysfunction, obvious dysfunction, and severe dysfunction). Participants' perception of loneliness was assessed through a single five category question: I have plenty of friends, and have not been lonely; although I have friends, I have been lonely occasionally; I have some friends but have been lonely for company; I have felt socially isolated and lonely; and not

known. Experienced stigma was assessed through a single question with response options no, yes, not known.

Demographic characteristics. Demographic characteristics comprised age, gender, marital status, education level, difficulty in reading/writing, employment status and participants' current living arrangements. Current living arrangements referred to the participant's place of residence at the time of the interview: public or private rented house/unit/apartment, family home, own house/unit, supported accommodation, homeless, institution/hospital, and other (including caravan or houseboat but not prison) (Harvey et al., 2012).

Disorder-related factors. Disorder-related factors comprised age of onset, diagnosis, presence of symptoms in the last 12-months, duration of illness, treatment and course of disorder (single episode with good recovery, multiple episodes with good recovery or with partial recovery, continuous illness without deterioration and continuous illness with deterioration).

Diagnoses were generated using the Diagnostic Interview for Psychosis (DIP) (Castle et al., 2006) and the associated Operational Criteria system for psychotic illness and affective illness (OPCRIT) computer algorithm (McGuffin et al., 1991). Items of the DIP selected for analysis included: any hallucinations, delusions, subjective thought disorder and depressive symptoms in the past 12-months. Negative symptoms were assessed, but without including aetiological attribution, using the items of the Carpenter Deficits syndrome (Kirkpatrick et al., 1989). Anxiety (manifested by worry, fear or panic attack) was coded no, yes, not known.

Treatment included the number of psychotropic (antipsychotics, mood stabilizers, antidepressants and anxiolytics) and anticholinergic medications used by a participant in the 4-weeks prior to interview. Medication or medication list were brought by participants to the interview (coded 0, 1, 2, 3, or 4 or more medications) (Waterreus et al., 2012); and 12-month

service utilization based on a 7-level hierarchy. This hierarchy comprised utilization of inpatient mental health (MH) admissions, specialized MH emergency services, emergency department with a MH problem, outpatient MH services, community MH services, attendance at a general practitioner for MH issues and "non-specified services", a category for participants not included in previous groups.

Physical health and trauma. Physical health refers to presence of lifetime asthma, allergies, chronic pain, CVD and/or diabetes, diagnosed by a doctor and self-reported during the interview. Trauma refers to the self-reported occurrence of any distressing or traumatic event during childhood other than separation/divorce of parents or loss of a parent, sibling or close relative (coded yes, no).

2.2. Statistical methods

Model building. A predictive model for HRQoL was built up using a "purposeful" selection strategy to arrive at a set of clinically meaningful, independent predictors. A set of variables was chosen *a priori* based on research evidence (Fig. 2) and sorted into six related groups: demographic characteristics; social experiences; diagnosis, symptoms and illness duration; treatment and course of disorder; physical health; and trauma. A three-stage model-building procedure was followed, as a way of deliberately selecting from a large set of possible covariates. At stage one, each variable was tested for a univariate association with HRQoL (AQoL-4D utility value) using linear regression. Variables were required to achieve both significance at $p < 0.05$ and the minimally important difference (MID) for the AQoL-4D (0.06) (Hawthorne and Osborne, 2005; Neil et al., 2018) for further consideration. At the second stage, models containing subsets of related variables (groups described above) were run, and variables failing to reach statistical significance at this stage were eliminated. At the third stage, retained variables from the subsets were combined in a full model, and again

variables were eliminated if not fulfilling significance and MID criteria: it was intended that only strongly significant and meaningful factors were represented in the final model.

Mediation analysis. To produce statistical evidence in support of a model of mediation, the traditional approach (Baron and Kenny, 1986) of comparing coefficients of the predictors of HRQoL before and after the inclusion of global functioning was used. The proportion of each effect attenuated was then noted.

Participants with missing values were excluded from the analyses (95.9% of the sample had complete data for the multivariable models). The statistical analysis was conducted using the statistical package Stata 15.0.

3. Results

3.1. Participants

1,642 participants met ICD-10 inclusion criteria for psychotic disorders. The sociodemographic and clinical characteristics of the participants are described in the supplementary tables S1 and S2. Over 60% of participants were male and were single/never married. The mean age was 38 years, the predominant diagnosis, schizophrenia. On average, the HRQoL of participants was half the maximum achievable value (i.e., 1.0) and they presented with marked difficulties in at least one of three areas of global functioning (socially useful activities, including work and study, personal and social relationships or self-care) or manifested difficulties in disturbing and aggressive behaviours in the previous 12 months. Three-fifths of participants were receiving two or more medications (psychotropics/anticholinergics) and over half reported a distressing or traumatic childhood event.

3.2. Linear regression analysis

Global functioning and 26 variables were tested as individual predictors of HRQoL; most achieved both, statistical significance at $p < 0.05$ and the MID for the AQoL-4D (Table 1). Exceptions were: age, gender, age of onset, duration of illness and diabetes. In the six models containing related subsets, marital status and education level in the demographic characteristics group, and asthma and allergies in the physical health group were not statistically significant. Education level and asthma also did not achieve the MID. Each of these variables was excluded from further analyses.

Please insert Table 1 around here.

Combining remaining variables in three groups (demographic characteristics and social experiences; disorder-related factors; physical health and trauma), positive symptoms and traumatic events in childhood did not achieve the MID, and diagnosis became not statistically significant. Each of these variables was excluded from further analyses. There were no issues with multicollinearity; no variable in any of the models had a variance inflation factor greater than 4.

All 14 significant variables were then combined in a composite group and assessed as predictors of HRQoL. Difficulty in reading/writing, employment, social dysfunction, experienced stigma, depressive symptoms, anxiety and service utilization became not significant. Thus, seven variables, namely perceived loneliness, number of negative symptoms, medication use, course of disorder, lifetime histories of chronic pain and CVD and current living arrangements had a meaningful independent effect on HRQoL measured with the AQoL-4D, with this model explaining 43% of the variance. The strongest predictors of HRQoL were perceived loneliness, number of negative symptoms, lifetime histories of chronic pain and CVD, with all greater than the MID and statistically significant.

3.3. Mediation analysis

Except for chronic pain, the identified predictors of HRQoL were associated with global functioning (Table 2). With inclusion of global functioning in a model with these predictors, 46% of the variance in HRQoL was explained, and evidence for partial mediation was found for five independent variables, with reductions in each of their total effects (Table 3). The two variables whose associations were not attenuated were perceived loneliness and chronic pain, and both retained an effect greater than the AQoL-4D MID.

Please insert Tables 2 and 3 around here.

Among the variables with evidence of mediation through global functioning, the largest reduction was seen in current living arrangements, for the group situated in an institution/hospital, with 53% of the independent effect on HRQoL attenuated after the addition of global functioning (Table 3). The second largest reduction was for the group with six negative symptoms (31%), followed by the groups with five (30%), four (29%), three (26%), two (23%) and one negative symptom(s) (20%). The groups of course of disorder with continuous illness without deterioration, as well as with deterioration, also presented a reduction in their coefficients (29% and 18% respectively). The smallest reduction was seen for CVD (13%) and the group that used four or more medications (12%).

4. Discussion

This study proposes the first theoretical model of the causal pathway of HRQoL in people with psychotic disorders based on the mediating effect of global functioning, and then establishes a statistical model. The theoretical model was based on an *a priori* understanding of predictors of HRQoL, including sociodemographic and clinical variables, as well as traumatic events in childhood. In the statistical model, predictors were required to achieve the MID for the AQoL-4D in addition to statistical significance for inclusion, allowing ascertainment of clinically meaningful, independent predictors of HRQoL in this population.

As hypothesized, global functioning was found to predict HRQoL of people with psychotic disorders, as did perception of loneliness, number of negative symptoms, course of disorder, number of medications (psychotropics/anticholinergics) used, a lifetime history of chronic pain or CVD, and current living arrangements. Our second hypothesis that independent predictors of HRQoL would include severity of symptoms (represented by the number of negative symptoms, but not depressive nor positive symptoms), and social experiences such as perception of loneliness was partially supported. Findings of effect attenuation on the HRQoL of participants for five of seven predictors after inclusion of global functioning provides evidence of partial mediation through global functioning for some predictors as hypothesized. However, no mediation was found for perceived loneliness, while lifetime history of chronic pain did not have an effect on global functioning and there was no evidence of effect diminution. These estimates of effect mediation need to be taken with some caution, given known limitations with the traditional Baron and Kenny method of estimating direct and indirect effects (Hayes, 2009; Richiardi et al., 2013). For example, a measurement error variable correlated with both functioning and HRQoL is omitted, and this has the effect of overestimating the indirect effects. Although we believe these effects to be small, stronger evidence could be obtained through a more sophisticated analysis that includes sensitive analyses. This could be conducted within a structural equation modelling framework, or the PROCESS methodology (Hayes, 2013).

Arguably the most interesting finding was the identification of perception of loneliness as the strongest predictor of HRQoL among study participants. In only one other study has perception of loneliness been considered as a predictor in a related population (Roe et al., 2011). Within Roe et al., perception of loneliness and social support were found to predict the QoL of people with schizophrenia and schizoaffective disorder in an examination of QoL as an independent moderator of the relationship between loneliness and social support

and self-reported recovery. Our result is also consistent with findings from Adewuya and Makanjuola's (2009) study in which perceived poor social support was found to predict the QoL of people with schizophrenia, although it was not the strongest predictor. The identification of loneliness as a predictor of HRQoL also extends our findings of the sensitivity of the AQoL-4D as a utility instrument that can capture variation in HRQoL associated with differences in loneliness (Nevarez-Flores et al., 2020).

Regarding the direct effect only of perception of loneliness on HRQoL, while perception of loneliness has been conceptualized as a subjective experience (Cacioppo and Patrick, 2008; Rokach, 2012) the PSP, used to assess global functioning, assesses performance of socially useful activities and personal and social relationships (i.e., objective aspects of social relationships). Thus, the results may be differentiating between an individual's objective capacity to socialize and the subjective quality they place on their social relationships. Together these findings reinforce the importance of social relationships for the HRQoL of people with psychotic disorders and support the inclusion of perception of loneliness in causal models for HRQoL in this population.

Number of negative symptoms was identified as the second strongest predictor of HRQoL in study participants and as giving rise to a dose-response effect. This finding contrasts with existing literature, in which negative symptoms were not identified as independent predictors of HRQoL (Alessandrini et al., 2016) nor of the mental or physical components of HRQoL (Lim and Lee, 2018; Vancampfort et al., 2015) when HRQoL was assessed with the 36-Item Short Form Survey Instrument (SF-)36. However, negative symptoms have been found to be predictors of both objective (Cruz et al., 2016) and subjective QoL (Suttajit and Pilakanta, 2015). The current findings thus confirm that negative symptoms are important determinants of HRQoL in addition to QoL in people with psychotic disorders, and that the AQoL-4D is sensitive to capturing variation in HRQoL based on the

number of negative symptoms (Neil et al., 2018). The observed partial mediation through global functioning was not surprising, as negative symptoms have been found to have an indirect effect on the HRQoL of people with schizophrenia via functioning (Alessandrini et al., 2016). Negative symptoms have also been found to be associated with poor functioning (Hunter and Barry, 2012) and to predict functional outcomes in this population (Ventura et al., 2009).

In contrast to previous studies that found depressive symptoms to be an independent predictor of HRQoL (Alessandrini et al., 2016; Chou et al., 2014; Stubbs et al., 2015) and of objective and subjective QoL (Kusel et al., 2007) in people with psychotic disorders, no independent effect for depressive symptoms was found in this study. It is postulated that the impact of depressive symptoms on HRQoL assessed within the current analysis could be attenuated by other included factors such as negative symptoms and perception of loneliness, as previously found by Świtaj et al. (2013). Further, loneliness, the strongest predictor of HRQoL in study participants, was not included in any of the above studies. Thus, some but not all symptoms are important independent predictors of HRQoL in this population when HRQoL is assessed with the AQoL-4D.

The independent effects associated with course of disorder (particularly for people with continuous illness) and with medication use also highlights the importance of severity of the disease for HRQoL. The strongest effect on HRQoL for medication use was found in people who used four or more medications, followed by people who did not use any medication. It was postulated that “no-medication” captures the impact of treatment non-compliance on HRQoL, while the use of four or more medications may be capturing the impact of treatment resistance and/or the presence of side effects. These postulations are in accordance with previous research that has found extrapyramidal symptoms (Yamauchi et al., 2008) and medical adherence (Stolovy et al., 2009) are predictors of subjective QoL, while

dose of antipsychotics predicts objective QoL (Yamauchi et al., 2008). With effects for course of disorder (whether or not continuous) and medication use partially mediated through global functioning, our results indicate these variables also should be considered in the causal pathway to achieve HRQoL in people living with psychosis. Highest level of service utilization in the last 12-months was not found to be an independent predictor of current HRQoL.

Among the physical health variables, a lifetime history of chronic pain and of CVD were found to be independent predictors of HRQoL. The finding for chronic pain is in agreement with previous literature that identifies bodily pain as a predictor of HRQoL in people with psychotic disorders (Stubbs et al., 2015). The absence of mediation for chronic pain was expected as the variable did not have an independent effect on global functioning (Table 2). Two factors could be influencing this finding. First, the pain threshold in people with schizophrenia is increased (Sakson-Obada, 2017), thus perceived pain may not be so severe as to affect global functioning. Second, most of the participants were using psychotropic medications, that are known to have hypoanalgesia effects, particularly the antipsychotics (Seidel et al., 2013).

To the best of our knowledge, no research has identified CVD as a predictor of HRQoL in this population, although a significant association between HRQoL assessed with the AQoL-4D and lifetime CVD and a cumulative effect of lifetime CVD and current depressive symptoms have been found (Neil et al., 2018). In contrast, other work has reported no differences in the HRQoL of people with schizophrenia-spectrum disorders with low/high CVD relative-risk when HRQoL was assessed using the SF-12 (Bressington et al., 2016). We also found that the effect of CVD on the study participants' HRQoL, was partially mediated through global functioning. Evidence on the effects of CVD on global functioning of people with psychosis is scarce. However, there is evidence of a bidirectional relationship between

mental disorders and CVD: psychosocial aspects can impact the cardiovascular system and CVD can impact brain, psychological function and general psychopathology (Levenson, 2018). As such, the effect of CVD on global functioning of study participants is not considered surprising. In addition, Azad et al. (2016) have reported that early diagnosis of CVD and CVD risk reduction are crucial to improving the QoL of people with schizophrenia. Thus, our findings provide evidence of the importance of CVD for both global functioning and HRQoL in people with psychotic disorders, and that CVD should be considered in the causal pathway to achieve HRQoL in people with psychotic disorder.

Living arrangements at the time of interview was also found to be a predictor of HRQoL, particularly for people situated in an institution/hospital. This finding is consistent with expectations of an association between living situation and QoL/HRQoL (Chan et al., 2003; Nevarez-Flores et al., 2020), with people situated in institutions or hospitals having the lowest QoL. Results of the mediation analysis highlighted findings for people situated in an institution/hospital, the only living arrangement group that predicted HRQoL and had its effect mediated through global functioning. Hospitalized people with schizophrenia typically have lower global functioning when compared with other accommodation groups (Chan et al., 2003) and people with psychosis in institutional settings present with higher disability in everyday, occupational and social functioning than other groups (Harvey et al., 2002). Thus, as housing has been recognized as an indicator of QoL (Harvey et al., 2002), it is not surprising that being situated in an institution or hospital is associated with direct and indirect effects on HRQoL through global functioning.

Consistent with the literature, age, gender (Stubbs et al., 2015) and age at onset (Norman et al., 2000) were not found to be predictors of HRQoL of people with psychotic disorders. Therefore, the results of this study suggested that these variables do not lie in the

causal pathway to achieve HRQoL, and do not need to be considered in statistical models of HRQoL for this population.

This study is the first to undertake an analysis to elucidate a statistical model that supports a causal path to achieve HRQoL based on the mediation effect of global functioning in people with psychotic disorders. Data from the 2010 National Survey of Psychosis, the largest survey of its kind in Australia and one of the most comprehensive epidemiological investigations into psychotic illness worldwide were analyzed. However, as this study has a cross-sectional design, causality cannot be established. Further, given constraints due to respondent burden (as more than 1500 items were included in the survey), some variables were assessed with a single question instead of multi-item instruments. However, as most of the assessments were used in the first survey, the Low Prevalence Disorders Study, it was considered that variables included in this study could appropriately provide a profile of the survey participants (Jablensky et al., 2000; 1999). For several variables that could potentially be confirmed through external sources, e.g., medical history, employment status and living arrangements, only patient self-report was available. As each interview was undertaken by a single interviewer, there is the potential for single-rater conflation of ratings. Finally, it is acknowledged that the strength of the results for loneliness, could be due to the use of the AQoL-4D which specifically assesses social relationships including loneliness. However, the importance of social components to people living with psychotic disorders has previously been described in the psychiatric literature.

This study presents a model that demonstrates that a variety of factors including objective (e.g., medications used) and subjective components (e.g., perception of loneliness) are affecting the HRQoL of people with psychotic disorders. These findings support the multidimensionality of HRQoL as a construct that includes both objective and subjective components, and that the AQoL-4D is an instrument that can capture this complexity.

In conclusion, evidence was presented in support of a credible causal pathway for HRQoL in people with psychotic disorders, mediated by global functioning. Global functioning was observed to attenuate the association of all predictors of HRQoL on HRQoL except perceived loneliness and lifetime experience of chronic pain, although noting the latter had no association with global functioning. This evidence can be used to support a mediation model of these predictors affecting HRQoL through global functioning. The predictor with the strongest relationship with HRQoL was perceived loneliness in the last 12-months, highlighting the importance of the quality of social relationships. Loneliness and the seven other identified predictors (global functioning, negative symptoms, course of disorder, medication use, current living arrangements (institutionalization), and lifetime histories of chronic pain and CVD) are each potential targets for improving the HRQoL of people with psychotic disorders. Clinicians and policy makers need to adopt a holistic approach in order to improve their patients' HRQoL, aiming to address relevant clinical and socio-environmental factors.

Fig. 1. Predictors of QoL reported in the literature.

Fig. 2. Theoretical model of HRQoL and the mediating role of global functioning.

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Table 1

Univariate associations between health-related quality of life and global functioning, social, demographic and clinical characteristics of the sample (n=1,613)

Variable	Constant	Coef.	95% CI	p value
PSP				
_cons	0.07		(0.02, 0.12)	
PSP		0.01	(0.01, 0.01)	<0.001
PSP (10-point interval)		0.08		
Age				
_cons	0.65		(0.60, 0.70)	
Age		-0.004	(-0.01, -0.003)	<0.001
Age (10 years)		-0.04		
Gender				
Male	0.50		(0.49, 0.52)	
Female		-0.004	(-0.03, 0.02)	0.759
Marital status				
Married or de facto	0.52		(0.48, 0.55)	
Single, never married		-0.000	(-0.04, 0.04)	1.00
Separated, divorced or widowed		-0.08	(-0.12, -0.03)	<0.01
Education level completed (n=1,594)				
Year 12	0.55		(0.52, 0.57)	
Year 11		-0.03	(-0.07, 0.01)	0.159
Year 10		-0.05	(-0.08, -0.01)	<0.05
Year 9 or below		-0.12	(-0.15, -0.08)	<0.001
Difficulty reading/writing				
No/NK	0.52		(0.51, 0.54)	<0.001
Yes		-0.11	(-0.15, -0.07)	<0.001
Employment (last 12-months)				
Employed	0.58		(0.55, 0.60)	
Volunteer/unpaid work		-0.02	(-0.07, 0.03)	0.902
Student		-0.06	(-0.13, 0.02)	0.256
No formal activity/Unemployed		-0.13	(-0.16, -0.10)	<0.01
Living arrangements at the time of the interview				
Family home	0.57		(0.54, 0.60)	
Public rented house/unit/apartment		-0.10	(-0.14, -0.06)	<0.001
Private rented house/unit/apartment		-0.06	(-0.10, -0.01)	<0.01
Own house/unit		-0.01	(-0.06, 0.04)	0.603
Supported accommodation		-0.13	(-0.18, -0.08)	<0.001
Homeless[a]		-0.10	(-0.16, -0.03)	<0.01
Institution/hospital		-0.26	(-0.36, -0.16)	<0.001
Other (but not prison)[b]		-0.12	(-0.26, 0.01)	0.076
Social dysfunction (last 12-months) (n=1,612)				
No dysfunction	0.64		(0.61, 0.66)	
Obvious dysfunction		-0.17	(-0.20, -0.14)	<0.001
Severe dysfunction		-0.29	(-0.33, -0.26)	<0.001
Perceived loneliness (last 12-months) (n=1,582)				
Plenty of friends, not lonely	0.67		(0.65, 0.70)	

Variable	Constant	Coef.	95% CI	p value
Friends, lonely occasionally		-0.08	(-0.12, -0.05)	<0.001
Some friends but lonely for company		-0.20	(-0.24, -0.16)	<0.001
Socially isolated and lonely		-0.41	(-0.45, -0.37)	<0.001
Experienced stigma (last 12-months) (n=1,609)				
No	0.55		(0.54, 0.57)	
Yes		-0.14	(-0.16, -0.11)	<0.001
Age of onset				
_cons	0.51		(0.47, 0.55)	
Onset		-0.00	(-0.002, 0.001)	0.793
Diagnosis ICD-10				
Delusional disorder	0.55		(0.49, 0.60)	
Schizophrenia		-0.03	(-0.09, 0.03)	0.377
Schizoaffective disorder		-0.06	(-0.12, 0.01)	0.096
Bipolar disorder with psychotic features		-0.04	(-0.10, 0.03)	0.286
Depressive psychosis		-0.22	(-0.31, -0.14)	<0.001
Positive symptoms (last 12-months)				
No	0.60		(0.57, 0.63)	
Yes		-0.12	(-0.16, -0.09)	<0.001
Number of negative symptoms (last 12-months)[c]				
0	0.70		(0.66, 0.73)	<0.001
1		-0.11	(-0.15, -0.06)	<0.001
2		-0.15	(-0.20, -0.10)	<0.001
3		-0.23	(-0.28, -0.18)	<0.001
4		-0.29	(-0.34, -0.24)	<0.001
5		-0.31	(-0.36, -0.26)	<0.001
6		-0.30	(-0.36, -0.25)	<0.001
Depressive symptoms (last 12-months)				
No	0.58		(0.56, 0.60)	
Yes		-0.14	(-0.17, -0.12)	<0.001
Anxiety (last 12-months) (n=1,595)				
No	0.57		(0.55, 0.58)	
Yes		-0.13	(-0.16, -0.10)	<0.001
Duration of illness				
_cons	0.57		(0.54, 0.59)	
Duration of illness		-0.004	(-0.01, -0.003)	<0.001
Psychotropic[d] and anticholinergic medications (last 4-weeks)				
One	0.56		(0.54, 0.59)	
None		-0.08	(-0.14, -0.03)	<0.01
Two		-0.06	(-0.10, -0.03)	<0.001
Three		-0.11	(-0.15, -0.07)	<0.001
Four or more		-0.17	(-0.23, -0.12)	<0.001
Mental health service utilization (last 12-months)[e]				
ED	0.60		(0.51, 0.68)	
Inpatient admission		-0.14	(-0.23, -0.05)	<0.01
Specialized emergency services		-0.13	(-0.23, -0.04)	<0.01
Community mental health services		-0.05	(-0.14, 0.04)	0.297

Variable	Constant	Coef.	95% CI	p value
Outpatient services		-0.05	(-0.15, 0.04)	0.266
GP MH		-0.14	(-0.25, -0.04)	<0.01
Non-specified services		-0.12	(-0.25, 0.001)	0.052
Course of disorder				
Single episode (good recovery)	0.63		(0.58, 0.68)	
Multiple episode (good recovery)		-0.03	(-0.09, 0.02)	0.256
Multiple episodes (partial recovery)		-0.15	(-0.20, -0.09)	<0.001
Continuous illness without deterioration		-0.20	(-0.26, -0.15)	<0.001
Continuous illness with deterioration		-0.31	(-0.37, -0.24)	<0.001
Asthma (lifetime) (n=1,608)				
No	0.52		(0.51, 0.54)	
Yes		-0.07	(-0.10, -0.04)	<0.001
Allergies (lifetime) (n=1,608)				
No	0.52		(0.50, 0.54)	
Yes		-0.07	(-0.10, -0.04)	<0.001
Chronic pain (lifetime) (n=1,608)				
No	0.55		(0.53, 0.56)	
Yes		-0.14	(-0.17, -0.11)	<0.001
Cardiovascular disease (lifetime) (n=1,606)				
No	0.52		(0.51, 0.54)	
Yes		-0.16	(-0.20, -0.12)	<0.001
Diabetes (lifetime) (n=1,595)				
No	0.51		(0.50, 0.53)	
Yes		-0.05	(-0.08, -0.01)	<0.01
Any distressing or traumatic event in childhood (n=1,593)				
No	0.55		(0.53, 0.57)	
Yes		-0.08	(-0.11, -0.05)	<0.001

Coef., coefficient; PSP, Personal and Social Performance Scale; NK, not known; ED, emergency department; GP MH, general practitioner mental health; CI confidence interval.

[a] Homeless. Primary: living on the streets, in parks or in deserted buildings; secondary: living in temporary shelters such as refuge, emergency accommodation or sleeping on friend's couch; tertiary: private boarding room.

[b] Including living in a caravan/houseboat.

[c] Without including aetiological attribution.

[d] Antipsychotics, mood stabilizers, antidepressants and anxiolytics.

[e] Highest level of service used.

Table 2
Multivariate associations between global functioning assessed with the PSP and predictors of health-related quality of life assessed with the AQoL-4D (n=1,590)

Variable	Constant	Coef.	95% CI	p value
	66.55		(63.37, 69.73)	<0.001
Living arrangements at the time of the interview				
Family home		*Ref.*		
Public rented house/unit/apartment		0.23	(-1.58, 2.04)	0.801
Private rented house/unit/apartment		4.87	(3.00, 6.75)	<0.001
Own house/unit		4.50	(2.34, 6.65)	<0.001
Supported accommodation		-7.20	(-9.53, -4.88)	<0.001
Homeless[a]		-0.61	(-3.61, 2.39)	0.689
Institution/hospital		-18.36	(-23.01, -13.71)	<0.001
Other (but not prison)[b]		-4.85	(-10.79, 1.08)	0.109
Perceived loneliness (last 12-months)				
Plenty of friends, not lonely				
Friends, lonely occasionally		2.27	(0.55, 3.99)	<0.05
Some friends but lonely for company		0.48	(-1.36, 2.32)	0.612
Socially isolated and lonely		-1.05	(-2.96, 0.85)	0.278
Number of negative symptoms (last 12-months)[c]				
0		*Ref.*		
1		-3.47	(-5.71, -1.24)	<0.01
2		-5.05	(-7.32, -2.78)	<0.001
3		-7.63	(-9.84, -5.42)	<0.001
4		-10.68	(-12.93, -8.43)	<0.001
5		-12.66	(-15.05, -10.26)	<0.001
6		-14.22	(-16.98, -11.46)	<0.001
Psychotropic[d] and anticholinergic medications (last 4-weeks)				
One		*Ref.*		
None		1.48	(-1.01, 3.97)	0.245
Two		0.45	(-1.01, 1.90)	0.546
Three		-1.07	(-2.93, 0.79)	0.259
Four or more		-3.20	(-5.59, -0.82)	<0.01
Course of disorder				
Single episode (good recovery)		*Ref.*		
Multiple episodes (good recovery)		-1.03	(-3.66, 1.59)	0.440
Multiple episodes (partial recovery)		-4.01	(-6.66, -1.35)	<0.01
Continuous illness without deterioration		-5.47	(-8.27, -2.67)	<0.001
Continuous illness with deterioration		-6.69	(-9.85, -3.53)	<0.001
Chronic pain (lifetime)				
No		*Ref.*		
Yes		-0.02	(-1.35, 1.30)	0.971
Cardiovascular disease (lifetime)				
No		*Ref.*		
Yes		-3.34	(-5.16, -1.51)	<0.001

Coef., coefficient; PSP, Personal and Social Performance scale; AQoL-4D, Assessment of Quality of Life four dimensions; CI, confidence interval.

[a] Homeless. Primary: living on the streets, in parks or in deserted buildings; secondary: living in temporary shelters such as refuge, emergency accommodation or sleeping on friend's couch; tertiary: private boarding room.

[b] Including living in a caravan/houseboat.

[c] Without including aetiological attribution.

[d] Antipsychotics, mood stabilizers, antidepressants and anxiolytics.

Table 3

Mediation analysis. Model I. Full multivariable model of predictors of health-related quality of life, excluding global functioning; Model II. Full multivariable model including global functioning (the mediator)

	Model I (N = 1,575)			Model II (N = 1,575)			Mediation	
	Coef. ß1	95% CI	p value	Coef. ß2	95% CI	p value	ß1-ß2	%[a]
Constant	0.899	(0.84, 0.95)		0.620	(0.54, 0.70)			
PSP				0.004	(0.003, 0.01)	<0.001		
Living arrangements at the time of the interview								
Family home	*Ref.*							
Public rented house/unit/apartment	-0.034	(-0.07, 0.00)	<0.05	-0.035	(-0.07, 0.00)	<0.05		
Private rented house/unit/apartment	-0.017	(-0.05, 0.02)	0.307	-0.037	(-0.07, 0.00)	<0.05		
Own house/unit	-0.004	(-0.04, 0.03)	0.849	-0.022	(-0.06, 0.02)	0.248		
Supported accommodation	-0.047	(-0.09, -0.01)	<0.05	-0.017	(-0.06, 0.02)	0.400		
Homeless[b]	-0.013	(-0.07, 0.04)	0.619	-0.010	(-0.06, 0.04)	0.696		
Institution/hospital	-0.146	(-0.23, -0.06)	<0.01	-0.068	(-0.15, 0.01)	0.099	-0.08	53%
Other (but not prison)[c]	-0.050	(-0.15, 0.06)	0.355	-0.029	(-0.13, 0.07)	0.582		
Perceived loneliness (last 12-months)								
Plenty of friends, not lonely	*Ref.*							
Friends, lonely occasionally	-0.075	(-0.11, -0.04)	<0.001	-0.084	(-0.11, -0.05)	<0.001		
Some friends but lonely for company	-0.161	(-0.19, -0.13)	<0.001	-0.163	(-0.19, -0.13)	<0.001		
Socially isolated and lonely	-0.332	(-0.37, -0.30)	<0.001	-0.327	(-0.36, -0.29)	<0.001		
Number of negative symptoms (last 12-months)[d]								
0	*Ref.*							
1	-0.075	(-0.11, -0.04)	<0.001	-0.060	(-0.10, -0.02)	<0.01	-0.01	20%
2	-0.092	(-0.13, -0.05)	<0.001	-0.071	(-0.11, -0.03)	<0.001	-0.02	23%
3	-0.126	(-0.17, -0.09)	<0.001	-0.094	(-0.13, -0.06)	<0.001	-0.03	26%
4	-0.156	(-0.20, -0.12)	<0.001	-0.111	(-0.15, -0.07)	<0.001	-0.05	29%
5	-0.178	(-0.22, -0.14)	<0.001	-0.124	(-0.17, -0.08)	<0.001	-0.05	30%

	Model I (N = 1,575)			Model II (N = 1,575)			Mediation	
	Coef. ß1	95% CI	p value	Coef. ß2	95% CI	p value	ß1-ß2	%[a]
6	-0.189	(-0.24, -0.14)	<0.001	-0.130	(-0.18, -0.08)	<0.001	-0.06	31%
Psychotropic[e] and anticholinergic medications								
One	*Ref.*							
None	-0.080	(-0.12, -0.04)	<0.001	-0.087	(-0.13, -0.04)	<0.001		
Two	-0.032	(-0.06, -0.01)	<0.05	-0.033	(-0.06, -0.01)	<0.01		
Three	-0.055	(-0.09, -0.02)	<0.01	-0.051	(-0.08, -0.02)	<0.01		
Four or more	-0.107	(-0.15, -0.06)	<0.001	-0.094	(-0.14, -0.05)	<0.001	-0.01	12%
Course of disorder								
Single episode (good recovery)	*Ref.*							
Multiple episodes (good recovery)	0.008	(-0.04, 0.05)	0.728	0.012	(-0.03, 0.06)	0.590		
Multiple episodes (partial recovery)	-0.042	(-0.09, 0.00)	0.075	-0.026	(-0.07, 0.02)	0.263		
Continuous illness without deterioration	-0.076	(-0.13, -0.03)	<0.01	-0.054	(-0.10, -0.01)	<0.05	-0.02	29%
Continuous illness with deterioration	-0.152	(-0.21, -0.10)	<0.001	-0.124	(-0.18, -0.07)	<0.001	-0.03	18%
Chronic pain (lifetime)								
Yes	-0.094	(-0.12, -0.07)	<0.001	-0.094	(-0.12, -0.07)	<0.001		
Cardiovascular disease (lifetime)								
Yes	-0.105	(-0.14, -0.07)	<0.001	-0.091	(-0.12, -0.06)	<0.001	-0.01	13%

Coef., coefficient; CI, confidence interval; PSP, Personal and Social Performance Scale.

[a] The independent effect mediated through global functioning is reported only for variables with a reduction in their total effect (and their total effect was greater than the minimally important difference 0.06).

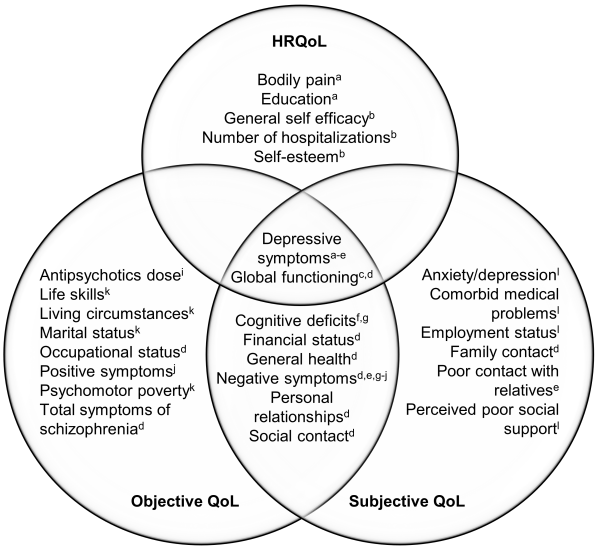
[b] Homeless. Primary: living on the streets, in parks or in deserted buildings; secondary: living in temporary shelters such as refuge, emergency accommodation or sleeping on friend's couch; tertiary: private boarding room.

[c] Including living in a caravan/houseboat.

[d] In the last 12-months, but without including aetiological attribution.

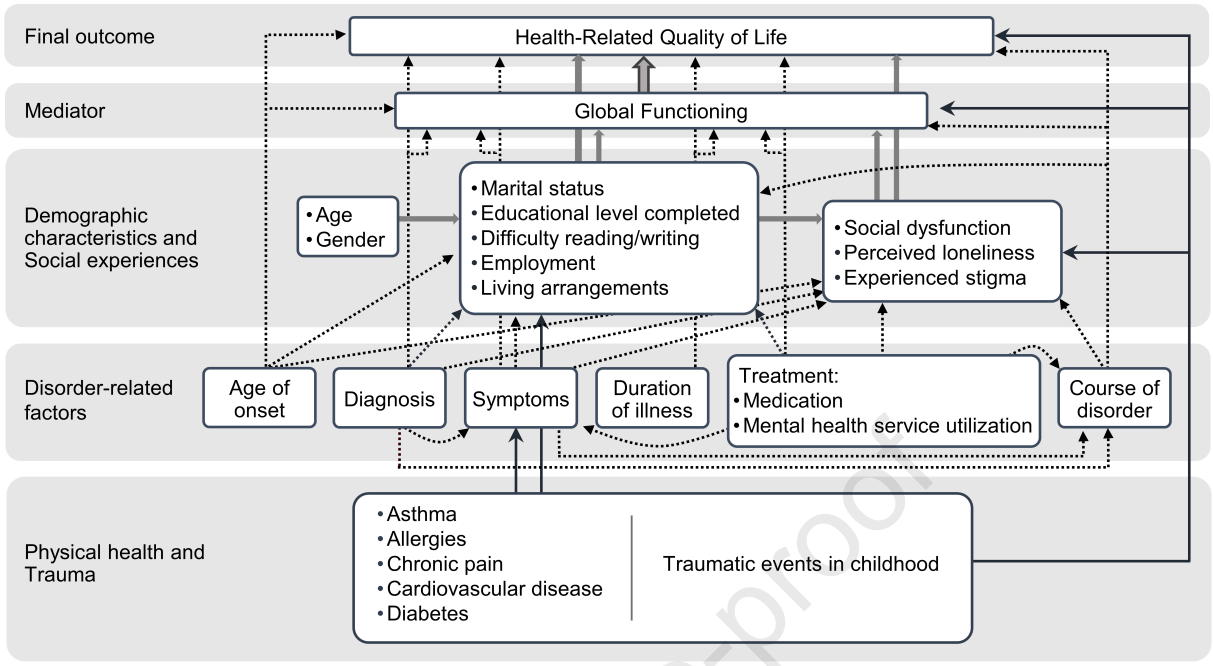
[e] Antipsychotics, mood stabilizers, antidepressants, and anxiolytics.

Predictors of HRQoL and QoL as reported in the literature



Note: Predictors are classified according to the instrument employed.
HRQoL, health-related quality of life; QoL, quality of life.

[a] Stubbs, 2015
[b] Chou et al., 2014
[c] Alessandrini et al., 2016
[d] Kusel et al., 2007
[e] Suttajit & Pilakanta, 2015
[f] Kurtz et al., 2012
[g] Cruz et al., 2016
[h] Aki et al., 2008
[i] Yamauchi et al., 2008
[j] Tomotake et al., 2006
[k] Norman, 2000
[l] Adewuya & Makanjuola, 2009



Note: Arrows show the direction in which variables could potentially affect other variables:
Physical health and Trauma ——
Disorder-related factors ·····
Demographic characteristics and Social experiences
Mediator

Declaration of competing interest

The authors have no conflict of interest.