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Effects of depression and cognitive impairment on quality of life in older adults with schizophrenia spectrum disorder: Results from a multicenter study.

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Conflicts of interests

FL has received speaker and consulting fees from AstraZeneca, Janssen, Lundbeck, Otsuka Pharmaceuticals, Roche and Servier, outside the submitted work. CL reports grants, personal fees and non-financial support from Lundbeck, personal fees from Servier and Daiichi-Sankyo, non-financial support from Otsuka Pharmaceuticals, outside the submitted work. AK reports personal fees from Eutherapie, Lundbeck, Otsuka and Janssen, unrelated to the submitted work. Other authors (RPDR, NH, CB, PL, YB, CVCL, HP) report no conflicts of interest relevant to the content of this article.

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Author Contributions Statement

RPDR, NH and FL designed the study. FL obtained the funding. RPDR and NH undertook statistical analyses. RPDR and NH wrote the first draft of the manuscript. PL, CB, AK, YB, CVCL, HP, CL and FL critically reviewed the manuscript. All authors contributed to and have approved the final manuscript.

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Abstract

Background: Little is known about the respective effects of depression and cognitive impairment on quality of life among older adults with schizophrenia spectrum disorder.

Methods: We used data from the Cohort of individuals with Schizophrenia Aged 55-years or more (CSA) study, a large multicenter sample of older adults with schizophrenia or schizoaffective disorder (N=353). Quality of life (QoL), depression and cognitive impairment were assessed using the Quality of Life Scale (QLS), the Center of Epidemiologic Studies Depression scale and the Mini-Mental State Examination, respectively. We used structural equation modeling to examine the shared and specific effects of depression and cognitive impairment on QoL, while adjusting for sociodemographic characteristics, general medical conditions, psychotropic medications and the duration of the disorder.

Results: Depression and cognitive impairment were positively associated ($r=0.24$, $p<0.01$) and both independently and negatively impacted on QoL (standardized $\beta=-0.41$ and $\beta=-0.32$, both $p<0.01$) and on each QLS quality-of-life domains, except for depression on instrumental role and cognitive impairment on interpersonal relations in the sensitivity analyses excluding respondents with any missing data. Effects of depression and cognitive impairment on QoL were not due to specific depressive symptoms or specific cognitive domains, but rather mediated through two broad dimensions representing the shared effects across all depressive symptoms and all cognitive deficits, respectively.

Limitations: Because of the cross-sectional design of this study, measures of association do not imply causal associations.

Conclusions: Mechanisms underlying these two broad dimensions should be considered as important potential targets to improve quality of life of this vulnerable population.

Key words: quality of life; schizophrenia; schizoaffective disorder; older adults; elderly; depression; cognition.

1. Background

Schizophrenia in late life is emerging as a major public health concern and very few large-scale studies have been conducted in the growing population of older adults with schizophrenia spectrum disorder. It is associated with reduced quality of life (QoL) and high rates of morbidity and mortality (Hoertel et al., 2014; Talaslahti et al., 2012; Tiihonen et al., 2009), which persist in later life (Cohen et al., 2015). Schizophrenia ranks third among psychiatric disorders as a cause of disability-adjusted life years in people aged 60 years or older (Whiteford et al., 2013).

Although some studies have shown that depression and cognitive impairment are highly prevalent (Cohen et al., 2015) and strongly associated with reduced QoL among older adults with schizophrenia spectrum disorder (Cohen et al., 1997; Cohen et al., 2008; Kasckow et al., 2010), important questions remain. First, to our knowledge, no study has examined the relative impact of these factors on QoL while adjusting for the confounding effects of sociodemographic factors (Cardoso et al., 2005; Harvey, 2001; Hasan and Tumah, 2019; Nyer et al., 2010), general medical factors (Diwan et al., 2007; Hsiao et al., 2012; Strassnig et al., 2003), psychotropic medications (Cardoso et al., 2005; Miyamoto et al., 2005) and the duration of the disorder (Hamaideh et al., 2014; Hsiao et al., 2012). Second, no study to our knowledge has examined whether QoL is influenced by depression and cognitive impairment in general, or by specific depressive symptoms or specific cognitive domains, or a combination of those explanations. This knowledge has important implications because it may help refine treatment models and guide public health policies to improve QoL and reduce disability and its associated costs in the growing population of older adults with schizophrenia spectrum disorder.

To address this gap in the literature, we used data from a large (n=353) study conducted at 63 centers in France, the “Cohort of individuals with Schizophrenia Aged 55

years or more” (CSA). Our aim was to examine the effects of depression and cognitive impairment on QoL among older adults with schizophrenia spectrum disorder. Because certain depressive symptoms or certain domains of cognitive functioning may differentially impact QoL, we used structural equation modeling to disentangle the shared and specific effects of depressive symptoms and symptoms of cognitive impairment on QoL in this population. All analyses were adjusted for potential confounders including sociodemographic factors (i.e., age, sex, education, marital status, parenthood and urbanicity), general medical factors (i.e., obesity, malnutrition, smoking, alcohol consumption and non-psychiatric medical conditions), psychotropic medications (i.e., atypical and typical antipsychotic medications, number of antipsychotics, antidepressants, benzodiazepines and anticholinergic antiparkinsonian medications) and the duration of the disorder.

2. Methods

2.1. Sample

Data were drawn from the CSA study (Abou Kassm et al., 2019; Hoertel et al., 2019; Schuster et al., 2019), a cohort of 353 inpatients (N=120, mean duration of hospitalization=134.7 days (SD=133.0)) or outpatients (N=233) aged 55 years or more with schizophrenia spectrum disorder, including people with schizophrenia (82.4%) or schizoaffective disorder (17.6%), whose age at onset of the disorder was before 40 years of age for 79.8% of the participants, between 40 and 60 years of age for 17.9% of them, and after 60 years for 2.3% of them. Participants were recruited between February 2010 and June 2013 from French state hospital psychiatric departments covering 63 mutually independent catchment areas (Raucher-Chéné et al., 2015). In France, state hospitalization services are organized into “sectors”. Each psychiatric sector is in charge of the mental health of a mutually independent catchment area comprising a mean population of 54,000 inhabitants

aged over 20 years, with a total of 839 sectors for adults across France (Verdoux, 2007). Each sector administers psychiatric beds in one French state hospital, which is either a general or a psychiatric hospital, and provides outpatient psychiatric treatment in Community Mental Health Centers (CMHCs), free of charge. Patients can also freely consult a private psychiatrist and choose to be hospitalized in another private or public hospital offering inpatient psychiatric care. Compulsory hospitalizations, however, have to take place in the French state hospital of the sector, apart from certain exceptions. The primary aims of this organization is to ensure that every individual living in France has easy access to mental health services and to promote the development of prevention and community care by an identified team (Verdoux, 2007). Additional details of the organization of the French mental health care system can be found elsewhere (Verdoux, 2007). In our study, inpatients were defined as patients who were hospitalized in a psychiatric inpatient unit at the time of the interview, whereas outpatients were those who were not hospitalized and were treated by a psychiatrist in a Community Mental Health Center. Exclusion criteria included limited French proficiency, being not affiliated to the social security system, meeting ICD-10 criteria for pervasive developmental disorder or major neurocognitive disorder and having any neurological disorder affecting the central nervous system. All participants were interviewed face-to-face by a psychiatrist to make the diagnosis and collect clinical data. The research protocol, including informed consent procedures, was conducted in accordance with the Declaration of Helsinki ethical guidelines and received full ethical review and approval from the local research ethics committee, the Advisory Committee on Information Processing in Material Research in the Field of Health and the National Board on Computerized Information and Freedoms (Hospital Clinical Research Program (PHRC) N°2008-N11-01). Written informed consent forms were obtained from all participants. This study includes all

the 353 participants aged 55 years or more with an ICD-10 diagnosis of schizophrenia or schizoaffective disorder.

2.2. Measures

2.2.1. Assessment of schizophrenia spectrum disorder, depression and cognitive functioning

Diagnoses of schizophrenia and schizoaffective disorder were made by the treating psychiatrist following ICD-10 criteria, independently of any prior diagnosis. Age at onset of first psychotic symptoms was also retrospectively investigated and duration of the disorder was estimated.

Depressive symptoms were self-reported by participants using the Center of Epidemiologic Studies Depression scale (CES-D). This 20-items questionnaire has been designed for use in community studies (Radloff, 1977). The CES-D asks participants how often they have experienced specific depressive symptoms during the previous week. Responses range from 0 ('hardly ever') to 3 ('most of the time'). The psychometric validity of this scale has been established in numerous general population samples (Airagnes et al., 2016; Matta et al., 2019; Radloff, 1977; Shafer, 2006), in samples of older adults (Irwin et al., 1999; Shafer, 2006) and in samples of subjects with psychiatric disorders (Furukawa et al., 1997; Herniman et al., 2017; Shafer, 2006; Zich et al., 1990) including schizophrenia spectrum disorders (Herniman et al., 2017). In our study, internal consistency reliability of the CES-D scale was acceptable, with Cronbach's $\alpha=0.72$. Based on the validation of the French version of the CES-D (Morin et al., 2011), a score ≥ 19 was used as primary indicator of depression. Continuous score of the CES-D was used also as a measure of severity.

Global cognitive functioning was evaluated by the investigator using the Mini-Mental State Examination (MMSE) (Robinson et al., 1975), a short assessment instrument widely

used for evaluating global cognitive impairment. In our study, internal consistency reliability of the MMSE scores was excellent (Cronbach's alpha= 0.93).

2.2.2. Evaluation of quality of life (QoL)

We used the Quality of Life Scale (QLS) (Heinrichs et al., 1984), an instrument commonly used in clinical studies of schizophrenia (Lehman, 1996). The QLS has 21 items rated on a 7-point scale from 0 to 6 with descriptive anchors, resulting in a range of 0-126 for the full scale; higher scores reflect greater QoL. Items explore 4 areas: instrumental role (occupational role, work functioning, work level, and work satisfaction), interpersonal relations (household, friends, acquaintances, social activity, social network, social initiative, withdrawal, and social and sexual behaviors), intrapsychic foundations (sense of purpose, motivation, curiosity, anhedonia, aimless inactivity, empathy, and emotional interaction), and common objects and activities. The sum of the mean scores from each area yields a total score. Higher scores signify higher QoL. The QLS has been designed to standardize and quantify the assessments about deficit symptoms typically made by clinicians treating patients with schizophrenia and is intended for use as an outcome criterion and a measure of change (Heinrichs et al., 1984). In our study, internal consistency reliability of the QLS was excellent (Cronbach's alpha=0.91).

2.2.3. Sociodemographic characteristics

Sociodemographic characteristics included sex, age, education (categorized as less than high school, high school, and college and higher), marital status (married or as if married versus not married), parenthood, and urbanicity (defined as living in an area comprising more than 1000 inhabitants per km²).

2.2.4. General medical conditions

General medical conditions included obesity (defined as having a body mass index (BMI) > 30 kg/m²), malnutrition (defined as having a body mass index < 23 kg/m²) (Winter et al., 2014), smoking status (smoking versus not smoking), alcohol consumption (consuming alcohol versus not consuming alcohol), and the number of non-psychiatric medical conditions.

2.2.5. Psychotropic medications

For all participants, all psychotropic medications (i.e., typical and atypical antipsychotic medications, number of antipsychotics, LA antipsychotic formulation, antidepressants, benzodiazepines and anticholinergic antiparkinsonian medications) prescribed at the time of the interview were recorded.

2.3. Statistical analyses

Percentages or means and their standard errors were estimated for the scores of the MMSE and CES-D and their subscales, sociodemographic characteristics, general medical conditions, psychotropic medications and the duration of the disorder across levels of QoL among older adults with schizophrenia spectrum disorder (**Table 1**). For descriptive statistics, we divided QoL into tertiles and analyzed it as a categorical variable. Multinomial regression models were used to examine the associations of QoL with potential predictors (**Table 2**).

We used confirmatory factor analysis (CFA) to identify the latent structure underlying the items of the MMSE. MMSE items were reverse coded to reflect cognitive impairment. Building upon the exploratory factor analysis (EFA) model fit by Jones et al. (Jones and Gallo, 2000), which identified five dimensions (concentration, language, orientation, attention and memory), we performed a second-order factor CFA model to determine whether a second-order factor (that we called ‘cognitive impairment’) measured by those five

dimensions fit the underlying the structure of items of the MMSE (**eTable 1**). Similarly, we used CFA to identify the latent structure underlying the items of the CES-D. Building upon the CFA model fit by Morin et al. (Morin et al., 2011), which identified four dimensions (depressed affects, positive affects, somatic complains and disturbed interpersonal relationships), we performed a second-order factor CFA model to determine whether a second-order factor (that we called ‘depression’) measured by those four dimensions fit the underlying the structure of items of the CES-D (**eTable 2**). We examined measures of goodness-of-fit, including the comparative fit index (CFI), the Tucker–Lewis index (TLI), and the root mean squared error of approximation (RMSEA). CFI and TLI values between 0.90 and 0.95 are considered acceptable, and CFI and TLI values greater than 0.95 and values of RMSEA lower than 0.06 indicate good model fit (Hu and Bentler, 1999).

Finally, we used structural equation modeling (SEM) (Hoertel et al., 2018a, 2018b, 2017, 2015a, 2015b; McMahan et al., 2018, 2015; Meneton et al., 2018; Pascal de Raykeer et al., 2018; Peyre et al., 2016) to examine the simultaneous effects of cognitive impairment and depression on QoL (used as a continuous variable) among older adults with schizophrenia. These models were adjusted for sociodemographic factors, general medical factors, psychotropic medications and the duration of the disorder.

To determine whether specific depressive symptoms or specific cognitive domains were associated with QoL above their shared effects represented in the models by latent factors, we calculated modification indices (i.e. chi-square tests with 1 degree of freedom) to test if any residuals were correlated with QoL. Statistical significance was evaluated using a two-sided alpha a priori set at 0.05. To reduce the risk of including significant direct effects related to multiple testing, we considered significant direct effects of items with modification index greater or equal to 10.

Missing data were imputed using Markov chain Monte Carlo (MCMC) methods (Schafer, 1997). Data were missing for at least 1 item of the CES-D scale, MMSE and QLS in 2.8% (N=10), 3.7% (N=13) and 37.1% (N=131) of participants, respectively. Global missing rate for QLS items was 23.9%. Exclusion of participants with missing data for at least 1 item of these scales resulted in a sample size of 211 participants. To examine the potential impact of missing data on our results, we performed two sets of analyses: (1) we imputed missing data using Markov chain Monte Carlo (MCMC) methods and (2) we performed sensitivity analyses while excluding participants with missing data. In the full sample of 353 participants, data were missing on the following covariates: urbanicity (1.4%, N=5), education (0.6%, N=2) and BMI (1.1%, N=4). Among the 211 participants with missing data for at least 1 CES-D, MMSE or QLS item, missing data rates for covariates were as follows: urbanicity (1.4%, N=3), education (0.5%, N=1) and BMI (1.0%, N=2). There were no missing data on the remaining variables included in our analyses. Exclusion of the few participants with missing data for any covariate (N=19 (5.4%) in the full sample of 353 participants and N=8 (3.6%) in the sample of the 211 participants with missing data for at least 1 CES-D, MMSE or QLS item) did not change the significance of our results.

Descriptive statistics were performed using PASW Statistics 18 software (IBM Corp., Armonk, NY, USA; released 2009). All SEM analyses were conducted using Mplus Version 7.3 (Muthen and Muthen, 1998-2006). The default estimator for the analysis was the variance-adjusted weighted least squares (WLSMV), a robust estimator appropriate for ordered categorical observed variables such as the ones used in this study (Muthen and Muthen, 1998-2006).

2.4. Supplementary analyses

Because cognitive impairment and depression may differentially impact the different quality-of-life dimensions explored by the QLS (i.e., instrumental role, interpersonal relations, intrapsychic foundations and common objects and activities), we repeated those analyses and examined the effects of cognitive impairment and depression across those quality-of-life domains. In addition, because clinical characteristics may differ between inpatients and outpatients (Way et al., 1992) and between institutionalized and non-institutionalized patients (Uggerby et al., 2011), we conducted SEM analyses while distinguishing successively these populations. In our study, institutionalization was defined as living in a dwelling that offers some form of formal supervision, including nursing homes, homes for the aged, hospital stays longer than 3 months, chronic care beds, and psychiatric institutions (Hébert et al., 2001). To examine the robustness of our results, we also performed sensitivity analyses while excluding participants with missing data.

3. Results

3.1. Quality of life (QoL), depressive symptoms and cognitive impairment among older adults with schizophrenia spectrum disorder

Among the 353 individuals, the mean QLS, MMSE and CES-D total scores were 52.0 (standard error of the mean (SEM)=1.1), 23.4 (SEM=0.3) and 16.7 (SEM=0.6). Multinomial logistic regression models showed that individuals with the lowest QoL were significantly more likely to be depressed, to have lower cognitive functioning, to be older and to have a higher number of non-psychiatric medical conditions (all $p < 0.05$) (**Tables 1 and 2**).

3.2. Structure of depressive symptoms and cognitive deficits

The second-order model of the 5 dimensions underlying the items of the MMSE provided a good fit to the data (CFI=0.985, TLI=0.984, RMSEA=0.032) (**eTable 1**), as did

the second-order model of the 4 dimensions underlying the structure of depressive symptoms (CFI=0.961, TLI=0.956, RMSEA=0.055) (**eTable 2**).

3.3. Effects of cognitive impairment and depression on QoL

The second-order factors ‘depression’ and ‘cognitive impairment’ were significantly and negatively associated with QoL ($\beta = -0.41$, $SE=0.04$, $p<0.01$ and $\beta = -0.32$, $SE=0.09$, $p<0.01$, respectively) (**Figure 1**). Depression and cognitive impairment were positively associated ($r=0.24$, $SE=0.05$, $p<0.01$). There was no significant direct effect from any first-order factors or any MMSE or CES-D item on QoL in addition. The magnitude of the effect of depression was significantly greater than that of cognitive impairment ($\beta = -0.41$ versus $\beta = -0.32$, $Wald=105.0$, $p<0.001$). Greater duration of the disorder, atypical antipsychotics and anticholinergic antiparkinsonian medications were significantly associated with cognitive impairment. Higher levels of educational attainment were significantly associated with better cognitive functioning and smoking was positively associated with depression. No other variable was significantly associated with QoL beyond the effects of depression and cognitive impairment.

3.4. Supplementary analyses

In sensitivity analyses excluding respondents with missing data for at least 1 item of the CES-D scale, MMSE and QLS (N=211), the mean QLS total scores were 52.5 (SEM=1.4). Multinomial logistic regression models showed that individuals with the lowest QoL were significantly more likely to be depressed and to have lower cognitive functioning (both $p<0.05$) (**eTables 3 and 4**). The second-order model of the 5 dimensions underlying the items of the MMSE provided a good fit to the data (CFI=0.984, TLI=0.982, RMSEA=0.032), as did the second-order model of the 4 dimensions underlying the structure of depressive

symptoms (CFI=0.946, TLI=0.939, RMSEA=0.065) (**eTables 5 and 6**). The pattern of associations between depression, cognitive impairment and quality of life was unchanged (**eFigure 1**).

We also found that depression and cognitive impairment negatively impacted all quality-of-life domains (**Figure 2**), although effects of depression on instrumental role and cognitive impairment on interpersonal relations did not reach a statistically significant level in sensitivity analyses excluding respondents with missing data, possibly because of lower statistical power (**eFigure 2**).

The mean QLS total scores in inpatients and outpatients were respectively 46.1 (SEM=1.9) and 54.1 (SEM=1.4) when using imputed data, and 47.1 (SEM=2.3) and 54.8 (SEM=1.7) when excluding respondents with missing data on at least 1 QLS, CES-D scale or MMSE item. The proportions of inpatients with schizoaffective disorder, late-onset schizophrenia (i.e., onset between 40 and 60 years of age) and very-late-onset schizophrenia (i.e., after 60 years) were 28.3%, 14.8% and 3.5% respectively, while these rates were 8.2%, 19.5% and 1.8% in outpatients. In sensitivity analyses distinguishing between inpatients and outpatients, we found a similar pattern of associations between depression, cognitive impairment and quality of life in both populations (**eFigures 3 to 6**). Among outpatients, depression and cognitive impairment negatively impacted on most quality-of-life domains (**eFigures 7 and 9**) whereas most of these effects did not reach a statistically significant level among inpatients, probably because of lower statistical power due to the limited number of inpatients in our study (**eFigures 8 and 10**).

The mean QLS total scores in institutionalized (N=124, 35.1%) and non-institutionalized (N=229, 64.9%) patients were respectively 44.8 (SEM=1.8) and 55.0 (SEM=1.5) (unequal variance t-test=-2.0 ; p-value=0.047) when using imputed data, and 44.5 (SEM=2.2) and 55.9 (SEM=1.7) (unequal variance t-test=-4.1 ; p-value<0.001) when

excluding respondents with missing data on at least 1 QLS, CES-D scale or MMSE item, supporting that institutionalization was significantly and substantially associated with diminished quality of life among older adults with schizophrenia spectrum disorder. In sensitivity analyses distinguishing between institutionalized and non-institutionalized patients, we found a similar pattern of associations between depression, cognitive impairment and quality of life in both populations (**eFigures 11 to 14**). In both samples of institutionalized and non-institutionalized patients, depression and cognitive impairment negatively impacted on most quality-of-life domains (**eFigures 15 to 18**).

4. Discussion

In a large multicenter sample of older adults with schizophrenia spectrum disorder, our results suggest that a second-order factor model describes well the structure underlying the items of the MMSE, as did a second-order model for the structure underlying the depressive symptoms assessed using the CES-D. We found that cognitive impairment and depression are interrelated and both are strongly associated with lower QoL, following adjustments for a wide range of potential confounders, including sociodemographic factors, general medical factors, psychotropic medications and the duration of the disorder. Their effects on QoL were not due to specific depressive symptoms or specific cognitive domains, but rather mediated through two broad dimensions representing the shared effects across all depressive symptoms and all cognitive deficits, respectively. These results held when excluding participants with missing data or considering the different quality-of-life domains explored by the QLS or distinguishing between inpatients and outpatients or between institutionalized and non-institutionalized patients, suggesting the robustness of our findings.

We found that cognitive impairment and depression are strongly related to lower QoL among older adults with schizophrenia spectrum disorder. Our results are in line with prior

studies (Cohen et al., 2015; Diwan et al., 2007; Jin et al., 2001; Vulser et al., 2018; Zisook et al., 1999) and extend their findings in suggesting that these associations are not due to specific depressive symptoms or specific cognitive domains, but rather related to broad dimensions representing shared mechanisms across all depressive symptoms and all cognitive deficits. These findings are consistent with data from behavioral and neuroimaging studies suggesting common mechanisms of co-occurring disorders such as schizophrenia and major depression (Anticevic et al., 2015; Barch et al., 2016; Network and Pathway Analysis Subgroup of the Psychiatric Genomics, 2015). Those studies suggest that factors related to neurotransmission, brain connectivity and genetic factors may constitute potential common mechanisms to explain comorbid depression in schizophrenia. Genome-wide association studies suggest that genes implied in histone methylation processes may be common risk factors for schizophrenia and depression (Network and Pathway Analysis Subgroup of the Psychiatric Genomics, 2015). A prior study (Barch and Ceaser, 2012) also reports that profiles of cognitive impairment may be very similar across schizophrenia, schizoaffective disorder and major depressive disorder with psychotic features, which would suggest common mechanisms leading to cognitive impairment in those disorders.

Our results highlight the importance of screening for depression and cognitive impairment in all older adults with schizophrenia or schizoaffective disorder and the potential important value of interventions targeting depression and cognitive impairment for improving QoL. For example, cognitive remediation therapy (Garrido et al., 2013; Wykes et al., 2011), social skill therapy (Almerie et al., 2015; Mueller et al., 2013), cognitive behavioral therapy (Dixon et al., 2010; Granholm et al., 2005) and antidepressants such as selective serotonin reuptake inhibitor (Kasckow et al., 2010; Zisook et al., 2009) have shown benefits to improving cognition (Goff et al., 2011; McGurk et al., 2007), mood (Bark et al., 2003; Bartels et al., 2014; Cohen et al., 2015; Dixon et al., 2010; Granholm et al., 2013; Kasckow et al.,

2010; Zisook et al., 2009) and quality of life (Cohen et al., 2011; Garrido et al., 2013; Kasckow et al., 2010; Zisook et al., 2009). Prior research (Cohen et al., 2015) has also suggested that physical activity, which is associated with cognitive improvement and depression alleviation, may also improve QoL (Leutwyler et al., 2014a; Leutwyler et al., 2014b).

Although both depression and cognitive impairment substantially influenced QoL in our study, we found that depression may have a significantly greater deleterious effect than cognitive impairment on QoL among older adults with schizophrenia spectrum disorder. Given its high prevalence and its potential negative impact on a wide range of outcomes such as suicidality (Hoertel et al., 2015a; Peyre et al., 2017; Zisook et al., 2007), cognition (Gupta et al., 2003; Irani et al., 2011; Kalache et al., 2015; Rajji and Mulsant, 2008; Twamley et al., 2002), community integration as well as on QoL (Cohen et al., 2015), depression should be systematically assessed and treated in all older patients with schizophrenia spectrum disorder, including those with cognitive impairment, in order to improve QoL as well as help reduce cognitive impairment, favor functional remission (Cohen et al., 2015) and prevent suicide risk.

Our results have several implications. From a clinical perspective, our results support the importance of screening for depression and cognitive impairment in all older adults with schizophrenia and schizoaffective disorder because there are both factors that are independently and substantially associated with decreased QoL. Our findings also support the importance to closely follow available guidelines when prescribing antipsychotics and anticholinergics parkinsonian medications in older adults with schizophrenia (Alexopoulos et al., 2004; Ogino et al., 2014) given their association with cognitive impairment in our study and others (Kawai et al., 2006; Takeuchi et al., 2013), and the importance of implementing existing programs targeting depression and cognitive impairment to improve QoL of this

vulnerable population. From an etiological perspective, our results support that effects of depression and cognitive impairment on QoL among older adults with schizophrenia are mainly mediated through two broad dimensions representing the shared effects across all depressive symptoms and all cognitive deficits, respectively. This finding underscores the importance of adopting dimensional approaches to depression and cognitive impairment to study their effect on QoL, which may help disentangle biological and psychological mechanisms underlying their associations.

Our study has several limitations. First, because of the cross-sectional design of this study, measures of association do not necessarily imply causal associations (Le Strat and Hoertel, 2011). Second, the recruiting psychiatric centers were all public-sector departments, which might have led to selection bias and decrease the generalizability of our findings. In addition, participants were recruited from 63 French state hospital psychiatric departments, each of them covering one mutually independent catchment area comprising a mean population of 54,000 inhabitants aged over 20 years, representing 7.5% of the total number of sectors in France (n=839) (Verdoux, 2007). Third, the MMSE provides a summary, rather than detailed assessment of cognitive function. Future studies could extend our results by conducting finer-grain examinations of cognitive deficits. Fourth, several factors known to influence quality of life, such as anxiety, living/social skills, medication side effects, life stressors, isolation, financial well-being, insight, religiousness, perceived well-being versus others/past self and physical activity (Cohen et al., 2017; Leutwyler et al., 2014a, 2014b) were not assessed in this study. Future studies would benefit in confirming our results while including these factors. Fifth, because each participant was interviewed by only one psychiatrist and participants were recruited from a large number of centers (n=63), we were unable to evaluate potential error variance in rating measurements. Sixth, despite the multicenter design of the study, the lack of random sampling might have led to selection bias. Seventh, major neurocognitive disorder, an

exclusion criterion, was assessed by the investigators, i.e., the treating psychiatrists, following ICD-10 criteria. However, the absence of standardized interview to screen for neurocognitive disorders may have resulted in underdiagnosing this comorbidity among study participants. In addition, causes of cognitive impairments were not assessed. Eighth, diagnoses of schizophrenia and schizoaffective disorder were made face-to-face by the treating psychiatrist following ICD-10 criteria, independently of any prior diagnosis. However, we did not record past diagnoses, preventing us to estimate diagnoses reliability. Ninth, our study did not include a matched cohort of healthy older adults, preventing us from determining whether the significance and the magnitude of the associations observed in older adults with schizophrenia spectrum disorder may be different or similar to those existing in healthy older adults. Future studies are needed to examine this issue. Tenth, the length of institutionalization, which may have a significant impact on depression, cognitive impairment and quality of life (Friedman et al., 2001), was not assessed in our study. Eleventh, even if major neurocognitive disorders were an exclusion criterion in our study, we cannot rule out that the accuracy of self-reported quality of life and depressive symptoms might be limited in a sample of older adults with schizophrenia who often have cognitive deficits and depressive symptoms. However, consistent with WHO's perspective on quality of life (Bachrach, 1996; The WHOQOL Group, 1998) and prior research (Bankole et al., 2007; Cohen et al., 2017), we chose to use a measure of quality of life that relies on self-appraisals and captures its multi-dimensionality. We used the Quality of Life Scale (QLS) (Heinrichs et al., 1984), an instrument commonly used in clinical studies of schizophrenia (Lehman, 1996), although it has not been specifically validated in this specific population to our knowledge. However, internal consistency reliability of the QLS was excellent in the full sample (Cronbach's $\alpha=0.91$), in the subsample of the 128 participants with a CES-D score ≥ 19 and in the subsample of the 161 participants with a MMSE score < 24 (Cronbach's $\alpha=0.91$ for both subsamples). The

psychometric validity of the CES-D scale used to assess depressive symptoms in our study has been established in numerous general population samples (Airagnes et al., 2016; Matta et al., 2019; Radloff, 1977; Shafer, 2006), in samples of older adults (Irwin et al., 1999; Shafer, 2006) and in samples of subjects with psychiatric disorders (Furukawa et al., 1997; Herniman et al., 2017; Shafer, 2006; Zich et al., 1990), including schizophrenia spectrum disorders (Herniman et al., 2017). In addition, internal consistency reliability of the CES-D was adequate in the full sample (Cronbach's $\alpha=0.72$) and in the subsample of the 161 participants with a CES-D score ≥ 19 (Cronbach's $\alpha=0.71$). Finally, depressive symptoms were self-reported rather than assessed using a standardized interview.

5. Conclusions

In a large multicenter sample of older adults with schizophrenia spectrum disorder, we found that cognitive impairment and depression are both strongly associated with lower QoL, independently of the sociodemographic and clinical characteristics. Their effects on QoL were not due to specific depressive symptoms or specific cognitive domains, but rather mediated through two broad dimensions representing the shared effects across all depressive symptoms and all cognitive deficits, respectively. Because effects of cognitive impairment and depression were mainly mediated through two broad dimensions, our results suggest that the mechanisms underlying these dimensions should be considered as important potential targets to improve quality of life of older adults with schizophrenia spectrum disorder.

6. References

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Table 1. Associations of depression, cognitive impairment, sociodemographic characteristics, general medical conditions, psychotropic medications, and the duration of the disorder with quality of life total score among older adults with schizophrenia spectrum disorder (N=353).

	Quality of life			
	Lowest tertile (N=118) (mean QLS=30.1, SEM=0.8)	Intermediate tertile (N=118) (mean QLS=49.9, SEM=0.5)	Highest tertile (N=117) (mean QLS=76.3, SEM=1.2)	Full sample (N=353) (mean QLS=52.0, SEM=1.1)
	% / Mean (SEM)	% / Mean (SEM)	% / Mean (SEM)	% / Mean (SEM)
Depression				
CES-D score ≥ 19				
Yes	58.3	31.6	21.9	37.3
No	41.7	68.4	78.1	62.7
CES-D continuous score	21.71 (0.98)	16.10 (1.05)	12.23 (0.77)	16.69 (0.58)
Depressed affects	6.21 (0.45)	4.30 (0.42)	3.18 (0.32)	4.57 (0.24)
Positive affects	6.88 (0.28)	5.19 (0.29)	4.62 (0.28)	5.57 (0.17)
Somatic complains	7.03 (0.37)	5.33 (0.41)	3.81 (0.32)	5.39 (0.22)
Disturbed interpersonal relationships	1.60 (0.16)	1.27 (0.15)	0.61 (0.13)	1.16 (0.09)
Cognitive impairment				
MMSE score	21.07 (0.55)	24.07 (0.40)	25.02 (0.37)	23.41 (0.27)
Concentration	1.96 (0.20)	3.23 (0.21)	3.36 (0.20)	2.86 (0.12)
Language	6.77 (0.13)	7.11 (0.12)	7.42 (0.11)	7.10 (0.07)
Orientation	7.80 (0.23)	8.84 (0.16)	9.22 (0.13)	8.63 (0.11)
Attention	3.71 (0.08)	3.85 (0.05)	3.93 (0.03)	3.83 (0.03)
Memory	1.73 (0.11)	2.13 (0.09)	2.22 (0.09)	2.03 (0.06)
Sociodemographic characteristics				
Age	68.59 (0.69)	66.64 (0.54)	66.33 (0.53)	67.19 (0.35)
Sex				
Women	52.5	41.5	60.7	51.6
Men	47.5	58.5	39.3	48.4
Education				

Less than high school	74.6	69.8	64.1	69.5
High school	14.4	17.2	14.5	15.4
College or higher	11.0	12.9	21.4	15.1
Marital status				
Single	87.3	87.3	80.3	85.0
Married or as if married	12.7	12.7	19.7	15.0
Parenthood				
Yes	36.4	37.3	47.9	40.5
No	63.6	62.7	52.1	59.5
Urbanicity				
Yes	80.3	67.5	82.1	76.7
No	19.7	32.5	17.9	23.3
General medical conditions				
Body mass index				
Obesity	23.5	27.1	33.6	28.1
Normal weight	44.3	48.3	40.5	44.4
Malnutrition	32.2	24.6	25.9	27.5
Smoking				
Yes	23.7	30.5	31.6	28.6
No	76.3	69.5	68.4	71.4
Alcohol consumption				
Yes	5.1	9.3	10.3	8.2
No	94.9	90.7	89.7	91.8
Number of non-psychiatric medical conditions	2.54 (0.16)	1.97 (0.14)	1.85 (0.14)	2.12 (0.09)
Psychotropic medications				
Antipsychotics				
None	7.6	5.1	11.1	7.9
Typical antipsychotics	44.9	46.6	46.2	45.9
Atypical antipsychotics	61.0	62.7	54.7	59.5
Antidepressants				
Yes	20.3	24.6	27.4	24.1
No	79.7	75.4	72.6	75.9
Benzodiazepines				
Yes	37.3	25.4	26.5	29.7
No	62.7	74.6	73.5	70.3
Anticholinergic				

antiparkinsonian medications				
Yes	33.1	35.6	35.0	34.6
No	66.9	64.4	65.0	64.5
Duration of the disorder	39.20 (1.30)	36.65 (1.24)	37.21 (1.13)	37.69 (0.71)

Abbreviations: SEM, standard error of the mean.

Note: quality of life was subdivided into tertiles, urbanicity was defined as living in an area comprising more than 1000 inhabitants per km², obesity and malnutrition were defined as having a body mass index >30 kg/m² and <23 kg/m², respectively.

Table 2. Associations of depression, cognitive impairment, sociodemographic characteristics, general medical conditions, psychotropic medications, and the duration of the disorder with quality of life among older adults with schizophrenia spectrum disorder (N=353).

	Quality of life		
	Lowest tertile vs. intermediate tertile	Lowest tertile vs. highest tertile	
	OR [95%CI] ^a / Wald	OR [95%CI] ^a / Wald	Likelihood-ratio chi-square test ^b
Depression			
CES-D score ≥19			
Yes	0.33 [0.19-0.57] / 16.04**	0.20 [0.11-0.36] / 29.55**	34.79**
No	1.00	1.00	
CES-D continuous score	0.95 [0.93-0.98] / 13.99**	0.91 [0.88-0.94] / 38.13**	47.60**
Depressed affects	0.91 [0.86-0.97] / 9.14**	0.85 [0.79-0.91] / 23.22**	27.68**
Positive affects	0.83 [0.76-0.91] / 16.13**	0.78 [0.72-0.86] / 27.13**	32.62**
Somatic complains	0.91 [0.85-0.97] / 8.76**	0.81 [0.75-0.87] / 31.22**	37.42**
Disturbed interpersonal relationships	0.90 [0.78-1.04] / 1.96	0.64 [0.53-0.78] / 19.45**	24.05**
Cognitive impairment			
MMSE score	1.13 [1.06-1.19] / 17.09**	1.19 [1.12-1.26] / 29.82**	38.71**
Concentration	1.31 [1.15-1.48] / 17.39**	1.34 [1.18-1.52] / 21.05**	27.06**
Language	1.20 [0.99-1.46] / 3.26	1.56 [1.23-1.98] / 13.40**	15.63**
Orientation	1.27 [1.11-1.46] / 11.64**	1.51 [1.28-1.80] / 22.60**	31.90**
Attention	1.36 [0.90-2.06] / 2.09	2.12 [1.14-3.94] / 5.68*	8.33*
Memory	1.40 [1.09-1.79] / 7.12**	1.53 [1.19-1.97] / 11.08**	13.04**
Sociodemographic characteristics			
Age	0.96 [0.92-0.99] / 5.09*	0.95 [0.91-0.99] / 6.80**	8.34*
Sex			8.75*
Women	0.64 [0.38-1.07] / 2.86	1.39 [0.83-2.34] / 1.58	
Men	1.00	1.00	
Education			5.83
Less than high school	1.00	1.00	
High school	1.28 [0.63-2.61] / 0.45	1.17 [0.56-2.46] / 0.18	
College or higher	1.25 [0.56-2.80] / 0.31	2.26 [1.08-4.72] / 4.68*	
Marital status			2.86

Single	1.00	1.00	
Married or as if married	1.00 [0.47-2.15] / 0.00	1.68 [0.83-3.41] / 2.06	
Parenthood			3.92
Yes	1.04 [0.61-1.76] / 0.02	1.60 [0.95-2.70] / 3.13	
No	1.00	1.00	
Urbanicity			7.84*
Yes	0.51 [0.28-0.93] / 4.84*	1.12 [0.58-2.16] / 0.11	
No	1.00	1.00	
General medical conditions			
Body mass index			4.31
Obesity	1.06 [0.56-2.00] / 0.03	1.57 [0.83-2.95] / 1.95	
Normal weight	1.00	1.00	
Malnutrition	0.70 [0.38-1.29] / 1.28	0.88 [0.47-1.64] / 0.16	
Smoking			2.15
Yes	1.41 [0.79-2.51] / 1.37	1.49 [0.84-2.64] / 1.82	
No	1.00	1.00	
Alcohol consumption			2.54
Yes	1.92 [0.69-5.37] / 1.54	2.13 [0.77-5.89] / 2.14	
No	1.00	1.00	
Number of non-psychiatric medical conditions	0.81 [0.69-0.95] / 6.82**	0.76 [0.65-0.90] / 10.05**	12.28**
Psychotropic medications			
Antipsychotics			
None	0.65 [0.22-1.88] / 0.63	1.51 [0.62-3.69] / 0.83	2.96
Typical antipsychotics	1.07 [0.64-1.79] / 0.07	1.05 [0.63-1.76] / 0.04	0.07
Atypical antipsychotics	1.07 [0.64-1.81] / 0.07	0.77 [0.46-1.30] / 0.96	1.73
Antidepressants			1.62
Yes	1.28 [0.69-2.36] / 0.61	1.48 [0.81-2.70] / 1.58	
No	1.00	1.00	
Benzodiazepines			4.77
Yes	0.57 [0.33-1.00] / 3.82	0.61 [0.35-1.06] / 3.13	
No	1.00	1.00	
Anticholinergic antiparkinsonian medications			0.19
Yes	1.12 [0.65-1.92] / 0.17	1.09 [0.64-1.88] / 0.10	
No	1.00	1.00	

Duration of schizophrenia	0.99 [0.97-1.01] / 2.18	0.99 [0.97-1.01] / 1.34	2.43
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^a Crude ORs indicate measures of association of quality of life with other variables and were estimated using multinomial logistic regression models; the reference group included individuals with the lowest quality of life.

Abbreviations: OR, odds ratio.

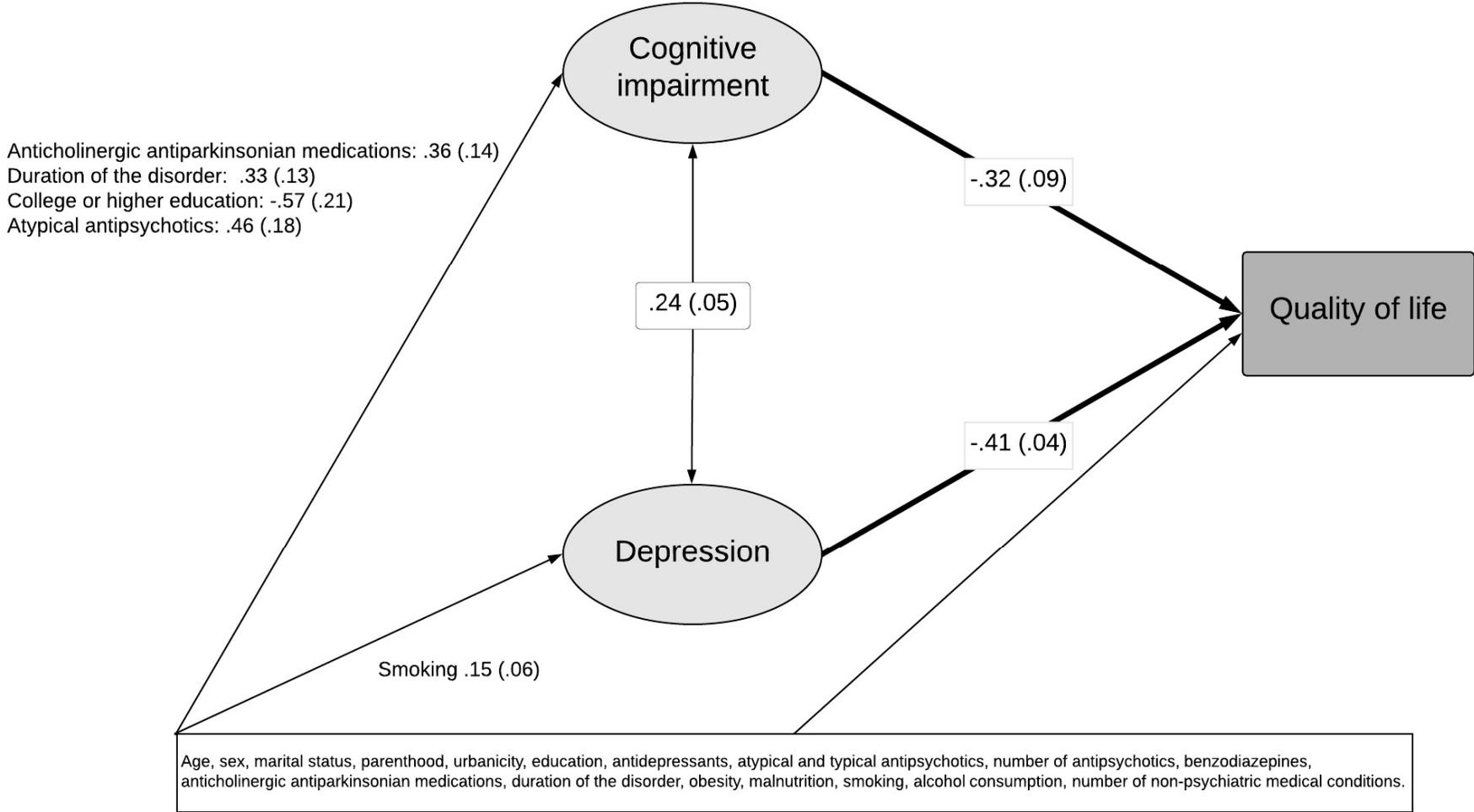
^b Likelihood-ratio chi-square tests examine whether at least one of the predictors' regression coefficient is not equal to zero in the model.

* p<.05; ** p<.01.

ORs/Wald/Likelihood-ratio chi-square test in bold are statistically significant with alpha set a priori fixed at 0.05.

Note: quality of life was subdivided into tertiles, urbanicity was defined as living in an area comprising more than 1000 inhabitants per km², obesity and malnutrition were defined as having a body mass index >30 kg/m² and <23 kg/m², respectively.

Figure 1. Effect of cognitive impairment and depression on quality of life among older adults with schizophrenia spectrum disorder (N=353).



Ellipses are used to denote latent constructs, rectangles are used to denote the observed variables impacting on these constructs.

MMSE items were reverse coded to reflect cognitive impairment. Cognitive impairment is a second-order latent construct measured by the five latent factors concentration, language, orientation, attention and memory which are measured by the items of the Mini Mental State Examination (MMSE).

Depression is a second-order latent construct measured by the four latent factors depressed affects, positive affects, somatic complains and disturbed interpersonal relationships which are measured by the items of the Center of Epidemiologic Studies Depression scale (CES-D).

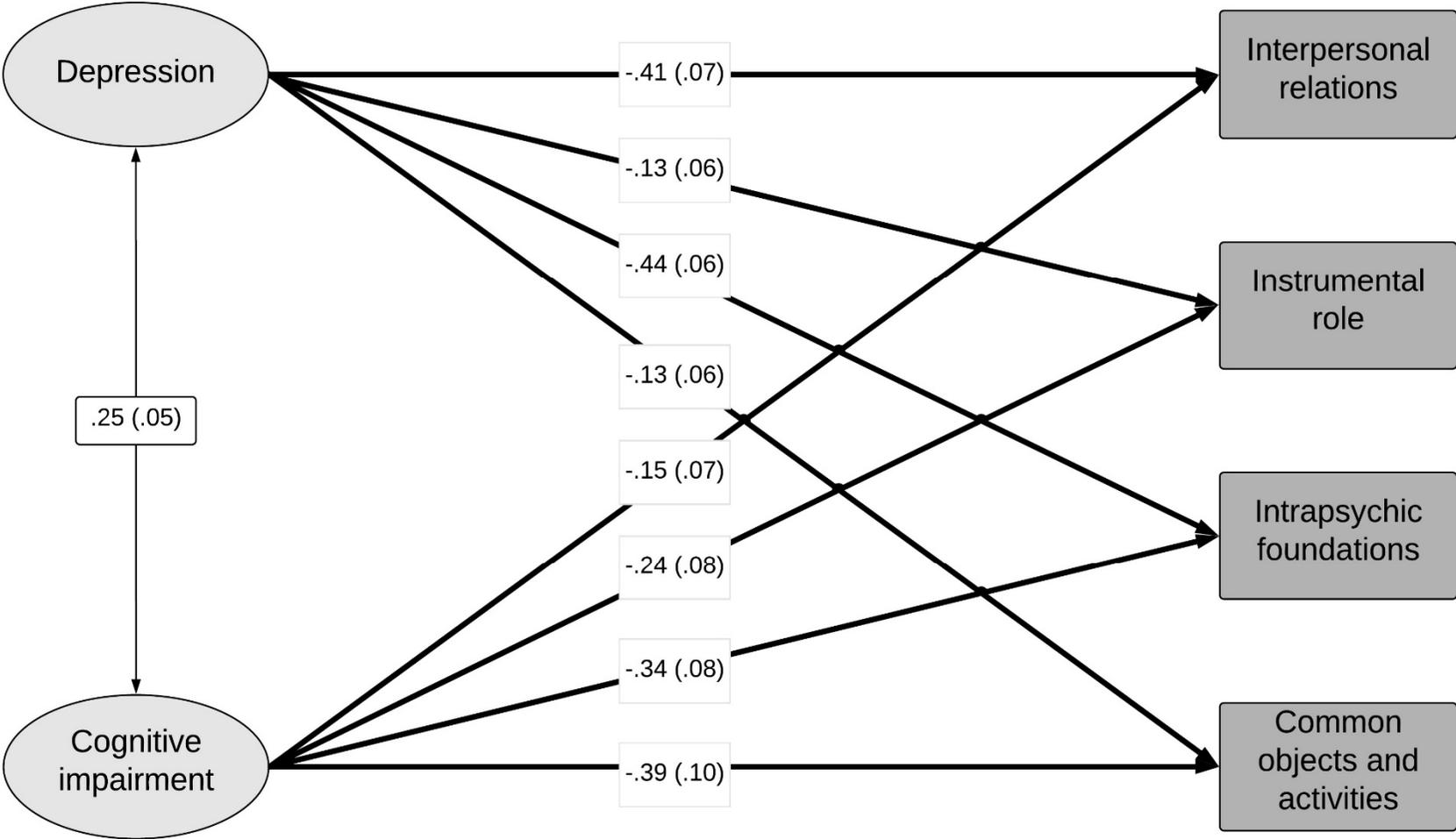
Regression coefficients shown are standardized and adjusted for sociodemographic factors (i.e., age, sex, education, marital status, parenthood and urbanicity), general medical factors (i.e., obesity, malnutrition, smoking, alcohol consumption and the number of non-psychiatric medical conditions), medications (i.e., atypical and typical antipsychotic medications, number of antipsychotics, antidepressants, benzodiazepines and anticholinergic antiparkinsonian medications) and the duration of schizophrenia.

Reference groups used for covariates are men, not married and not living with someone as if married, with normal weight, with less than high school education, with no child, living in an area of less than 1000 inhabitants per km², non-smokers, alcohol abstainers, not receiving antidepressants, benzodiazepines, typical or atypical antipsychotics, or anticholinergic antiparkinsonian medications.

Only significant effects (two-sided $p < 0.05$) are represented in the model.

There was no significant direct effect from any other factor or any CES-D or MMSE item in addition (all modification indices < 10).

Figure 2. Effects of cognitive impairment and depression across quality-of-life domains among older adults with schizophrenia spectrum disorder (N=353).



Ellipses are used to denote latent constructs, rectangles are used to denote the observed variables impacting on these constructs.

Residuals of quality-of-life domains were allowed to correlate with each other.

MMSE items were reverse coded to reflect cognitive impairment. Cognitive impairment is a second-order latent construct measured by the five latent factors concentration, language, orientation, attention and memory which are measured by the items of the Mini Mental State Examination (MMSE).

Depression is a second-order latent construct measured by the four latent factors depressed affects, positive affects, somatic complains and disturbed interpersonal relationships which are measured by the items of the Center of Epidemiologic Studies Depression scale (CES-D).

Regression coefficients shown are standardized and adjusted for sociodemographic factors (i.e., age, sex, education, marital status, parenthood and urbanicity), general medical factors (i.e., obesity, malnutrition, smoking, alcohol consumption and the number of non-psychiatric medical conditions), medications (i.e., atypical and typical antipsychotic medications, number of antipsychotics, antidepressants, benzodiazepines and anticholinergic antiparkinsonian medications) and the duration of schizophrenia. Reference groups used for covariates are men, not married and not living with someone as if married, with normal weight, with less than high school education, with no child, living in an area of less than 1000 inhabitants per km², non-smokers, alcohol abstainers, not receiving antidepressants, benzodiazepines, typical or atypical antipsychotics, or anticholinergic antiparkinsonian medications.

Only significant effects (two-sided $p < 0.05$) are represented in the model.

There was no significant direct effect from any other factor or any CES-D or MMSE item in addition (all modification indices < 10).