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**Major depression, sleep, hostility and body mass index are associated with impaired quality of life in schizophrenia. Results from the FACE-SZ cohort.**

Running title: sleep, hostility and depression and quality of life in schizophrenia

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**Abstract** (limited 250)

**Background.** Impaired Quality of life (QoL) in schizophrenia has been mostly associated with psychotic and mood symptomatology, insight and functioning so far.

**Aims.** QoL levels remain unsatisfactory due to other factors we aim to explore.

**Method.** We have explored sleep quality with the Pittsburgh Sleep Quality Index, hostility with the Buss&Perry questionnaire, major depression with the Positive and Negative Syndrome Scale depressive factor, functioning with the Global Assessment of Functioning scale and weight gain with body mass index in addition to other classical QoL-associated factors.

**Results.** 559 patients (mean age=31 (SD 9) years, 74% male sex) were included in the national FACE-SZ cohort. impaired QoL has been significantly associated with respectively major depression, impaired sleep quality, increased hostility, impaired functioning and impaired insight independently of age, sex, treatments, tobacco smoking and body mass index.

Major depression was associated with impaired psychological and physical well-being, and impaired self-esteem. Impaired sleep quality has been associated with impaired psychological and physical well-being and sentimental life. Hostility has been associated with impaired psychological well-being and self-esteem, impaired friends' relationships and impaired autonomy. Weight was associated with impaired physical well-being. Tobacco smoking was associated with higher level of friends' relationships.

**Conclusions.** Major depression, sleep, hostility, and weight gain have been identified as potential targets to improve QoL in schizophrenia and should be implemented in the recommendations for good practice to optimize schizophrenia care.

**Declaration of interest.** None.

**Keywords:** psychiatry, quality of life, schizophrenia, sleep quality, hostility, major depression, weight.

## Introduction

SZ is still associated with deeply impaired QoL despite decades of research focusing on residual psychotic/mood symptomatology, impaired daily functioning, high insight into illness and internalized stigma [1–7]. While no systematic review has synthesized data on quality of life in schizophrenia (SZ) so far, SZ remains the psychiatric disorder with the highest loss of quality-adjusted life years (QALYs) [8]. Identifying new factors associated with impaired quality of life (QoL) in schizophrenia (SZ) is a priority [4] and is now possible by assessing a large sample of our national FACE-SZ cohort.

Major depression has been already identified as the most important feature for impaired SZ QoL [4,9]. Yet we don't know so far if this association is independent of sleep and hostility that are symptoms of major depression and frequent in SZ patients. Sleep was associated with impaired QoL in an exploratory Israeli study published in 2004 independently of depression in 145 SZ patients[10]. A Portuguese study published in 2013 reported among 811 SZ patients, impaired sleep being associated with lower life satisfaction[11]. A Chinese study carried out in 623 SZ outpatients found an association of sleep and mental QoL (assessed by the SF-12 scale) but not physical QoL in SZ patients[12]. These results were replicated in a recent Spanish study [13]. Yet these four studies reported limitations due to sample sizes or no adjustment for potential confounding factors including age, sex and illness characteristics. A standardized sleep evaluation has been implemented in the FACE-SZ cohort in 2015[14], which is a timely opportunity to address this issue.

Hostility may be the second culprit for impaired QoL in SZ. Hostility is a core dysfunction that may explain persecutory delusions and impaired functioning in schizophrenia [15]. Hostility has been associated with impaired QoL in FACE-SZ patients independently of positive and negative symptoms[16–18], and more specifically with impaired friends' relationships [19]. These findings were reinforced by targeting hostility showing effectiveness in improving life satisfaction but only in non-remitted SZ patients[20]. Yet hostility was mostly explored as a clinician-rated single symptom with no dedicated scale, which is a limit of these results.

Major depression was also found to be associated with high weight gain risk[21] and weight gain has been associated with impaired QoL in schizophrenia[22,23].

In summary, preliminary data suggested to explore sleep, hostility, and weight in addition to depression to identify new targets to improve SZ QoL. The bottleneck was the lack of large-scale standardized data so far but is now possible thanks to our FACE-SZ cohort. The objective was thus to determine if sleep quality, hostility, major depression and weight were independently associated with impaired QoL impairment in stabilized SZ outpatients and to determine which QoL area may be specifically concerned.

## **Population and methods**

### **Study design, study population, diagnosis, ethical concerns**

The FACE-SZ cohort has been described in previous articles [14,24]. The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is based on a French national network of 10 Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles), set up by a scientific cooperation foundation in France, the FondaMental Foundation ([www.fondation-fondamental.org](http://www.fondation-fondamental.org)) and pioneered by the French Ministry of Research in order to create a platform that links thorough and systematic assessment to research [24].

### **Study population**

#### **Inclusion criteria**

Consecutive clinically stable patients (defined by no hospitalization and no treatment changes during the 8 weeks before evaluation) with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder were consecutively included in the study. Diagnosis was confirmed by two trained psychiatrists of the Schizophrenia Expert Centres network. All patients were referred by their general practitioner or psychiatrist who subsequently received a detailed evaluation report with suggestions for personalized interventions.

#### **Exclusion criteria**

All patients with other diagnoses than schizophrenia (except for major depression, anxiety disorder, eating disorder and addictions) and those not speaking French were excluded.

### **Diagnosis**

Patients were interviewed by members of the specialized multidisciplinary team of the Expert Center. Diagnoses interviews were carried out by two independent psychiatrists according to the Structured Clinical Interview for Mental Disorders (SCID 1.0) module B to H (Psychotic and associated symptoms, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders and eating disorders).

### **Ethical concerns**

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki). The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18th, 2010). All data were collected anonymously. As this study include data coming from regular care assessments, a non-opposition form was signed by all participants.

### **Collected data**

All scales were used in their French version. The psychometric properties and the rationale for the choice of the scales are described in [24].

QoL was assessed using the SQoL-18 questionnaire, a self-administered, multidimensional instrument developed and validated for the specific assessment of QoL in SZ patients [25,26] with 18 items describing eight dimensions: Psychological Well-being, Self-Esteem, Family Relationships, Friends' relationships, Resilience, Physical Well-being, Autonomy, and Sentimental Life, as well as a total score. Dimensions and total scores range from 0, indicating the lowest QoL, to 100, indicating the highest QoL. Internal consistency was satisfactory (item-internal consistency greater than 0.40; Cronbach's alpha coefficients ranged from 0.72 to 0.84). The scalability was satisfactory, with INFIT statistics within an acceptable range [26].

### Confounding variables

Sociodemographic and clinical characteristics (age, sex, education level, age at illness onset) were reported. Education level was a continuous variable (number of years of scholarship from primary school).

### Variables hypothetically influencing QoL

Major depression was assessed with the Positive and Negative Syndrome Scale for Schizophrenia depressive factor[27]. The internal consistency of this five-factor structure was good (Cronbach's alpha >0.70) in the relapse and chronic patients [28]. No threshold has been determined so far [27,28].

Daily functioning and current illness severity were assessed with the Global Assessment of Functioning scale (GAF) [29].

The PANSS total score was not included as too collinear with the PANSS depressed factor. Positive and negative symptoms were proxy by the GAF score, which includes symptoms severity.

Sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI) [30,31]. This 19-item self-questionnaire generated a total score ranging from 0 to 21. We used the validated French version [32]. A total score equal or above 5 is in favor of sleep disturbances with clinical significance. The PSQI has not been validated in SZ patients but was used in most of previous studies exploring sleep disturbances in SZ [33–36] and has been validated in other psychiatric disorders [37,38]. The PSQI demonstrated adequate internal consistency in post-traumatic disorder with Chronbach's  $\alpha=0.72$ [41].

Hostility was measured by the Buss-Perry Aggression Questionnaire (BPAQ) hostility score. While it has not been specifically validated in schizophrenia, BPAQ is a widely used self-rated measure showing internal consistency and stability over time[39]. Retest reliability for the BPAQ over 9 weeks was satisfactory [40]. The BPAQ hostility demonstrated adequate internal consistency in post-traumatic disorder with Chronbach's  $\alpha=0.77$ [40].

Insight was measured by the Birchwood Insight Scale score, a brief self-reported measure with Chronbach's  $\alpha=0.75$  [42,43]. Current daily tobacco smoking was self-reported. Alcohol use disorder (the presence of at least 2 symptoms among the 11 explored in DSM-5 indicates an Alcohol Use Disorder) was evaluated with the



Structured Clinical Interview for Mental Disorders (SCID 1.0) (module E substance use disorders) [44].

Body mass index (BMI) calculated as weight in kilograms divided by the square of the height in meters.

Treatments were reported. The antipsychotic treatments were classified according to their Anatomical-Therapeutic-Clinical ATC class. First-generation antipsychotics (FGA) were defined by ATC class N05AA to AC (phenothiazines), NO5AD (butyrophenones), NO5AF (thioxanthenes). Second-generation antipsychotics (SGA) were defined by ATC class N05AH (diazepines, oxazepines, thiazepines and oxepines) and NO5AL (benzamides)[45].

### **Statistical analyses**

The aim was to explore the association of QoL with the following variables (developed in the rationale): PSQI score, BPAQ hostility score, PANSS depressed factor, Birchwood score, GAF score, body mass index. The following variables were included in the analyses as potential confounding factors: age, education level, age at illness onset, sex, tobacco smoking, alcohol current disorder, first/second generation antipsychotics.

Univariate analyses. Socio-demographics, clinical characteristics, QoL and treatments are presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. We performed bivariate analyses to select variables in the multivariate analyses. Associations between S-QoL 18 total score and the continuous variables (age, education level, age at illness onset, PSQI score, BPAQ hostility score, PANSS depressed factor, Birchwood score, GAF score, body mass index) were analyzed using Pearson's and Spearman's correlation tests. Means-based comparisons of the S-QoL 18 total score between various subgroups (sex, tobacco smoking, alcohol current disorder, first/second generation antipsychotics) were performed using student-t and Mann-Whitney tests. were analyzed using Pearson's and Spearman's correlation tests. Means-based comparisons of the S-QoL 18 total score between various subgroups (sex, tobacco smoking, alcohol current disorder, first/second generation antipsychotics).

Then multivariate analyses using multiple linear regression were performed to determine QoL-associated variables selected from the previous univariate S-QoL 18 total score analysis based on a threshold  $p\text{-value}\leq 0.20$ . As classical significance levels, such as 0.05, can fail to identify important variables, we chose a  $p$ -value cut-off point of 0.2 for the selection process of variables in a multivariate model [46–48]. The S-QoL 18 total score and each of its dimensions were considered as separate dependent variables. Tobacco smoking was forced because of being reported in more than an half of stabilized outpatients and its association with a wide range of poor health outcomes [21,49].

The final models incorporated the standardized  $\beta$  coefficients, which represent a change in the standard deviation of the dependent variable (QoL) resulting from a change of one standard deviation in the various independent variables. The independent variables with the higher standardized beta coefficients are those with a greater relative effect on QoL. The statistical significance level was set at  $p<0.05$  for a two-sided test, except for the multivariate analysis ( $p\leq 0.01$ ) to reduce the chance of false positive. Data were analyzed using SPSS 17.0 software (SPSS Inc., Chicago, IL).

## Results

Overall, 559 patients (mean age=31+/-9 years, 74% male sex) have been consecutively included in the FACE-SZ cohort. Sample characteristics are presented in **Table 1**, univariate analyses in **Table 2**.

In multivariate analyses (**Table 3**), impaired QoL has been significantly associated with respectively impaired sleep quality, increased hostility, major depression, impaired functioning and impaired insight independently of age, sex, treatments, tobacco smoking and body mass index. More specifically, impaired sleep quality has been associated with impaired psychological and physical well-being. Hostility has been associated with impaired psychological well-being and self-esteem, impaired friends' relationships and impaired autonomy. Major depression was associated with impaired psychological and physical well-being and impaired self-esteem. Body mass index was associated with impaired physical well-being. Tobacco smoking was associated with higher level of friends' relationships.

## **Discussion**

The analysis of the FACE-SZ enabled us to identify sleep, hostility, depression and body mass index as independent factors associated with impaired QoL in SZ. Future studies should determine if improving these factors may improve QoL in SZ.

Sentimental life is the most impaired area of SZ QoL, yet no intervention to date aim at helping SZ patients to recover a satisfying sentimental life. We have recently identified sexual dysfunctions in >40% of stabilized SZ outpatients [50,51]. Future studies should determine the role of sexual dysfunctions in SZ sentimental life.

Depression was associated with impaired QoL in FACE-SZ independently of sleep and hostility. This confirms our previous findings in FACE-SZ[4], yet we analyzed depression in a quantitative manner in the present analyses and with PANSS depressive factor instead of Calgary Depression Rating Scale (with a cut-off of 6 defining major depression). This suggests that even low/residual depression may be associated with impaired QoL. Depression is frequent and undertreated in SZ<sup>38</sup>. Depression has been associated with impaired physical well being in our results, which may be mediated by physical pain previously identified in one of five FACE-SZ patients[53].

We confirmed that sleep was associated with a wide range of impaired psychological and physical well being, consistently with previous studies[10,11,54,55]. As mentioned in the rationale, the association between impaired sleep and well being was well documented in non-SZ populations[56] but in SZ we still don't know the respective association of sleep and depression with QoL. To exceed this limit, our results were adjusted for depression [35]. Future studies should determine if improving sleep may improve QoL in SZ patients. Strategies improving sleep in SZ may be divided in two types: (1) Among pharmacological approaches, some sedative antipsychotics may improve sleep through antihistaminic action[57], yet they also increase diurnal sedation and diminish physical activity, inducing weight gain. Weight gain may impact physical well-being, which may lead to a vicious circle [58]. Hypnotics are addictive and not recommended in the long-term [59]. Future studies should determine if pharmacological approaches may improve sleep with a good benefit/risk ratio in SZ. (2) Among non-pharmacological approaches, psychoeducation, third-wave behavioral and cognitive therapies, decreased screen

exposure before sleep, diurnal physical activity, tobacco/cannabis cessation and alcohol reduction remain insufficiently developed in SZ patients despite their potential efficacy to improve SZ QoL [6,9,13].

Hostility was associated with a wide range of impaired QoL domains in FACE-SZ (including relationships with friends and sentimental life, impaired self-esteem and psychological well being and impaired autonomy) consistently with previous studies [16–20]. Interventions targeting hostility may be also divided in pharmacological and non-pharmacological interventions. (1) Among pharmacological approaches, the following interventions have been classified in order of evidence for efficacy: paliperidone-extended release, clozapine, propranolol, valproate and famotidine[60]. Benzodiazepine cessation may also improve hostility[61] (2). Among non-pharmacological strategies, cognitive and behavioral therapies have shown efficacy[62]. The evidence for family intervention remains insufficient in this domain[63]. As for sleep, future studies should confirm if improving hostility may improve SZ QoL

Body mass index was also associated with impaired physical well being in our results independently of depression and treatments. This association was shown for the first time due to lack of previous explorations on this issue in schizophrenia. Combined with above-mentioned results, body-orientated therapies showing effectiveness in non-SZ populations (e.g. weight loss, nutrition, physical activity, yoga [64–66]) appear of peculiar interest in SZ patients with impaired physical well being and should be further tested.

Current daily tobacco smoking was associated with better friends relationships, which may indicate the prosocial effect of smoking (sharing smoking activity with others) and may also explain the difficulties for quitting smoking [67]. These issues should be addressed by specific interventions programs addressing the need for prosocial strategies for isolated SZ patients.

Limits and perspectives. Due to the cross-sectional design of the study, no causal relationship can be inferred from the results. The PSQI and Buss&Perry scale should be validated in schizophrenia in future studies. Neuroticism, physical activity, internalized stigma and stigma resistance have not been explored in FACE-SZ to avoid the patients' assessment overburden while they have been associated with impaired QoL in SZ [68–70]. Genetic variations have been identified in sleep disorders in SZ patients and should be further explored [71].

Strengths. The multivariate models enabled us to determine four independent factors for improving QoL in SZ: sleep, hostility, depression and body mass index. Multiple confounding factors were explored and the significant level was set at 0.01 to avoid type 1 error. Each dimension was assessed with dedicated standardized scales, especially PSQI for sleep and Buss&Perry for hostility, which strengthens the quality of these results. The use of structured interviews for alcohol disorders diagnoses may be mentioned as another strength.

## **Conclusion**

Analyzing FACE-SZ has revealed that sleep, hostility, depression and body mass index may be targeted to improve quality of life (including psychological and physical well being) in SZ patients. These four targets remain therapeutic challenges for clinicians, patients and families to date with no available guidelines and insufficient therapeutic intervention evaluations. Developing effective programs is urgently needed to improve their effectiveness and thus the QoL of SZ patients.

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## **Conflicts of interest**

None declared.

**Contributors**

GF and LB performed the statistical analysis. GF and LB wrote the first complete manuscript. All authors were involved in the patients' recruitment, the clinical evaluation, acquisition of the clinical data, modified the manuscript and approved the final version.

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**Table 1.** Sample characteristics (N=559).

		N (%) or Mean (SD)
<b>Socio-demographic characteristics</b>		
Age (years)		31.3 (9.0)
Sex	Men	414 (74.1)
	Women	145 (25.9)
Education level (years)		12.3 (2.6)
<b>Clinical characteristics</b>		
Age at illness onset		21.2 (6.3)
Pittsburgh Sleep Quality Index		6.6 (3.4)
Buss&Perry hostility score		22.4 (6.9)
PANSS depressed score		7.3 (3.2)
Insight Birchwood score		9.0 (2.9)
Functioning and current illness severity (GAF score)		50.9 (14.2)
Current daily tobacco smoking	Yes	285 (52.9)
	No	254 (45.4)
Current Alcohol use disorder	Yes	42 (7.5)
	No	517 (92.5)
Body mass index		26.6 (5.6)
<b>Treatment characteristics</b>		
First generation antipsychotics	Yes	123 (22.0)
	No	436 (78.0)
Second generation antipsychotics	Yes	429 (76.7)
	No	130 (23.3)
<b>Quality of life*</b>		
S-QoL 18 index		52.9 (17.9)
Psychological Well-being		55.0 (26.4)
Self-Esteem		48.4 (29.0)
Family relationships		70.7 (25.3)
Friends relationships		52.7 (27.8)
Resilience		56.3 (27.3)
Physical Well-being		45.2 (26.7)
Autonomy		59.3 (26.2)
Sentimental Life		35.4 (30.0)

\* Quality of life: Scores range from 0 to 100; higher scores represent higher QoL.

**Table 2.** Factors associated with S-QoL 18 index: univariate analysis.

		S-QoL 18 index M or R	SD	p-value
Age (years)		-0.09		0.022
Sex	Men	52.3	17.5	0.167
	Women	54.7	18.9	
Education level (years)		-0.02		0.714
Age at illness onset		-0.05		0.297
Pittsburgh Sleep Quality Index		-0.37		<0.001
Buss&Perry hostility score		-0.38		<0.001
PANSS depressed score		-0.44		<0.001
Insight Birchwood score		-0.20		<0.001
Functioning and current illness severity (GAF score)		0.28		<0.001
First generation antipsychotics	Yes	49.6	16.6	0.024
	No	53.8	18.2	
Second generation antipsychotics	Yes	53.2	17.5	0.436
	No	51.8	19.2	
Current daily tobacco smoking	Yes	52.5	17.1	0.539
	No	53.4	18.8	
Current Alcohol use disorder	Yes	51.1	18.9	0.509
	No	53.0	17.8	
Body mass index		-0.09		0.072

M± SD : mean± standard deviation ; R: Spearman's correlation coefficient.

**Table 3.** Factors associated with S-QoL 18 index and dimensions QoL scores: multivariate analyses.

	S-QoL 18 index β	Psychological Well- being β	Self- Esteem β	Family Relationships β	Friends Relationships β	Resilience β	Physical Well-being β	Autonomy β	Sentimental Life β
Age (years)	-0.06	-0.01	-0.03	-0.12 <sup>‡</sup>	-0.07	-0.05	0.02	-0.04	0.00
Sex	-0.06	-0.08	-0.01	0.01	-0.04	-0.09	-0.01	0.03	-0.12 <sup>‡</sup>
Pittsburgh Sleep Quality Index	-0.19 <sup>**</sup>	-0.16 <sup>**</sup>	-0.11 <sup>‡</sup>	-0.10	-0.08	-0.08	-0.22 <sup>**</sup>	-0.05	-0.14 <sup>‡</sup>
Buss&Perry hostility score	-0.22 <sup>**</sup>	-0.16 <sup>**</sup>	-0.22 <sup>**</sup>	-0.10	-0.22 <sup>**</sup>	-0.05	-0.11 <sup>‡</sup>	-0.22 <sup>**</sup>	-0.10
PANSS depressed score	-0.19 <sup>**</sup>	-0.23 <sup>**</sup>	-0.36 <sup>**</sup>	0.03	-0.01	-0.12 <sup>‡</sup>	-0.15 <sup>**</sup>	-0.10	-0.06
Insight Birchwood score	-0.19 <sup>**</sup>	-0.13 <sup>**</sup>	-0.14 <sup>**</sup>	-0.02	-0.07	-0.13 <sup>**</sup>	-0.19 <sup>**</sup>	-0.15 <sup>**</sup>	-0.16 <sup>**</sup>
Functioning and current illness severity (GAF score)	0.17 <sup>**</sup>	0.14 <sup>**</sup>	0.06	-0.02	0.15 <sup>**</sup>	0.15 <sup>**</sup>	0.06	0.16 <sup>**</sup>	0.16 <sup>**</sup>
First generation antipsychotics	0.01	-0.08	-0.01	0.10	0.06	-0.04	-0.04	0.00	0.04
Body mass index	-0.02	0.02	-0.02	0.01	-0.03	0.02	-0.14 <sup>**</sup>	0.08	-0.04
Current daily tobacco smoking	0.02	0.05	0.03	-0.00	0.13 <sup>**</sup>	-0.09	-0.04	0.03	-0.01
adjusted R-squared	0.32	0.27	0.35	0.02	0.11	0.14	0.22	0.15	0.12

S-QoL 18 : Scores range from 0 to 100; higher scores represent higher QoL. PANSS total score and other subscores were not included in the analyses due to collinearity with PANSS depressed factor. Current illness severity was proxy by the GAF scores which includes both positive/negative symptoms and functioning

β: standardized beta coefficient (β represents the change of the standard deviation in QoL score resulting from a change of one standard deviation in the independent variable)

\*  $p \leq 0.05$ . \*\*  $p \leq 0.01$ .