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## **Redefining peripheral inflammation signature in schizophrenia based on the real-world FACE-SZ cohort.**

Running title: peripheral inflammation in schizophrenia

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**Abstract** (limited 250)

**Background.** Peripheral inflammation is associated with impaired prognosis in schizophrenia (SZ). Highly sensitive C-reactive protein (hs-CRP) is the most used inflammatory biomarker in daily practice. However, no consensual cut-off has been determined to date to discriminate patients with peripheral inflammation from those without.

**Aims.** To determine if patients with peripheral inflammation between 1 and 3 mg/L had poorer outcomes compared to those with undetectable CRP (<1mg/L).

**Method.** Consecutive participants of the FACE-SZ cohort with a hs-CRP<3 mg/L were included in 10 expert academic centers with a national geographical distribution between 2010 and 2018. Potential sources of inflammation, socio-demographics, illness characteristics, current illness severity, functioning and quality of life and were reported following the FACE-SZ standardized protocol.

**Results.** 580 patients were included, of whom 226 (39%) were identified with low-grade inflammation defined by a hs-CRP between 1 and 3mg/L. Overweight and lack of dental care were identified as potential sources of inflammation. After adjustment for these factors, patients with inflammation had more severe psychotic, depressive and aggressive symptomatology and impaired functioning compared to the patients with undetectable hs-CRP. No association with tobacco smoking or physical activity level has been found.

**Conclusions.** Patients with schizophrenia with hs-CRP level between 1 and 3 mg/L should be considered at risk for inflammation-associated disorders. Lowering weight and increasing dental care may be useful strategies to limit the sources of peripheral inflammation. Hs-CRP>1mg/L is a reliable marker to detect peripheral inflammation in patients with schizophrenia.

**Declaration of interest.** None.

**Keywords:** psychiatry; schizophrenia; inflammation; quality of life.

## 1. Introduction

One of the major discoveries of the three last decades in psychiatry was the role of inflammation in schizophrenia (SZ)(Khandaker et al., 2015). High-quality meta-analyses have recently synthesized these findings(Bora, 2019; Fraguas et al., 2019;

Marques et al., 2018; Orlovska-Waast et al., 2019). In summary, SZ individuals have immune-inflammatory dysfunctions from their first psychotic episode, before antipsychotic treatment onset (Fraguas et al., 2019). This peripheral inflammation may induce increased blood-brain barrier permeability with a subsequent neuroinflammation, leading to neuroprogression, cognitive decline and impaired functioning (Bora, 2019). In mirror, anti-inflammatory strategies have shown effectiveness in the treatment of schizophrenia (Çakici et al., 2019). Improving the treatment of schizophrenia in a precision medicine approach would therefore need to identify patients with low-grade peripheral inflammation to implement anti-inflammatory strategies in these patients. However, the definition of the clinical signature of inflammation remains a persistent question. How should clinicians discriminate SZ patients with inflammation from those without it?

The C-reactive protein (CRP) is the most frequent inflammatory marker used in clinical practice. The increase of CRP is the common final marker of multiple inflammatory cascades, including Interleukin-6, Interleukin-1 and Tumor Necrosis Factor (TNF) pathways. The interleukin-6 pathway has been shown to be disturbed in all phases of schizophrenia (Goldsmith et al., 2016). Moreover, CRP is a good marker of central inflammation (i.e. neuroinflammation) (Felger et al., 2018). A highly-sensitive dosage of CRP (hs-CRP) has been developed to detect low-grade inflammation, until 1 mg/L. The remaining question is thus the cut-off that should be chosen to discriminate patients with or without peripheral inflammation. Most of the studies have chosen a cut-off of 3mg/L based on the US recommendations identifying patients with hs-CRP $\geq$ 3mg/L at high risk of myocardial event (for review see (Guillaume Fond et al., 2018)). However, a hs-CRP between 1 and 3 mg/L was considered as a grey zone at intermediate risk of myocardial event (Ridker Paul M, 2003). We still don't know if these patients with a hs-CRP level between 1 and 3 mg/L are at increased risk of inflammation-associated poor outcomes.

Our hypotheses were that patients with a hs-CRP levels between 1 and 3 were at increased risk of poor outcomes associated with peripheral inflammation, including positive, negative and depressive symptoms and impaired functioning (Fond et al., 2016, 2017b; G. Fond et al., 2018; Fond et al., 2019, 2021). We also hypothesized that higher tobacco smoking levels, overweight or obesity would be associated with increased peripheral inflammation (Fond et al., 2017a; Godin et al., 2017)

The aim of the present study was to determine if SZ patients with peripheral inflammation defined by a [1-3]mg/L blood hs-CRP level were at increased risk of inflammatory-associated poor outcomes compared to those with undetectable hs-CRP

levels (<1mg/L).

## **2. Population and methods**

The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is a national cohort of stabilized SZ outpatients followed-up for ten years and recruited in 10 Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles) ([www.fondation-fondamental.org](http://www.fondation-fondamental.org)) (Schürhoff et al., 2018, 2015).

### **2.1 Study population**

*Inclusion criteria.* Consecutive clinically stabilized 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.

### **2.2 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) (First MB, et al, n.d.) module B to H (Psychotic and associated symptoms, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders and eating disorders).

### **2.3 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 was collected anonymously. As this study include data coming from regular care assessments, a non-opposition form was signed by all participants.

## **2.4 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 (Schürhoff et al., 2015).

### *Peripheral inflammation definition*

High sensitivity CRP (hs-CRP) was measured with an assay using nephelometry (Dade Behring). As developed in the rationale, abnormal CRP level was defined as  $\geq 1\text{mg/L}$ . The clinicians and the patients were blinded of the peripheral inflammation status at the time of evaluation. Laboratory personnel were blinded to the clinical evaluation at the time of CRP assay.

### *Sociodemographics,*

Sociodemographic data (age (years), sex (binary), education level) were reported. Education level was a continuous variable (number of years of scholarship from primary school).

### *Potential sources of inflammation*

The potential sources of inflammation were explored according to the literature data in SZ and non-SZ populations. Antipsychotics and antidepressants have been suggested to modulate inflammation in schizophrenia (Fonseka et al., 2016; Kappelmann et al., 2018; Maes et al., 2000; Meyer et al., 2009). 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), N05AD (butyrophenones), N05AF (thioxanthenes). Second-generation antipsychotics (SGA) were defined by ATC class N05AH (diazepines, oxazepines, thiazepines and oxepines) and N05AL (benzamides) (Misdrahi et al., 2019). Chlorpromazine equivalent doses (CPZ100eq) were calculated according to the minimum effective dose method (Leucht et

al., 2014). Mood stabilizers, benzodiazepines, and three classes of antidepressants were reported (selective serotonin reuptake inhibitors, serotonin and norepinephrine inhibitors and tricyclic agents).

Physical activity was self-reported by the addition of the weekly duration of moderate and intense physical activity according to the World Health Organization definition<sup>34,35</sup>.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Abdominal perimeter was measured in cm. Current constipation, diarrhea and history of gastrointestinal ulcer were reported (binary answers). The following data were collected during the expert center evaluation: high blood pressure, HDL cholesterol (mM), LDL cholesterol (mL), diagnosed diabetes (binary), fasting glucose (mM), glycated hemoglobin (%), triglyceridemia (mM), uric acid ( $\mu\text{mol/L}$ ). Serum uric concentrations were determined by spectrophotometry.

History of dental care in the last 12 months and current daily tobacco smoking were self-reported (binary answer).

Alcohol and cannabis use disorders were defined according to the SCID IV-TR (First MB, et al, n.d.). Coffee consumption was also recorded (number of cups/week).

The following inflammatory diseases were reported from medical reports and corresponding physicians: asthma, lupus erythematosus, Crohn disease, psoriasis, multiple sclerosis, rheumatoid arthritis, any type of cancer.

#### *Illness characteristics and current illness severity*

Illness characteristics included age at illness onset (years), age at first antipsychotic treatment (years), duration of untreated psychosis defined by [age at first antipsychotic treatment – age at illness onset] (years).

Psychotic symptomatology was assessed with the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) and extrapyramidal symptoms with the Extrapyramidal Rating Scale (Simpson & Angus, 1970). Depressive symptoms were assessed with the Calgary Depression Rating Scale for Schizophrenia (CDRS) (Addington et al., 1993)). This scale was specifically designed to identify specific depressive symptomatology that cannot be related to negative symptoms of schizophrenia. Current major depressive episode was defined by a CDRS score  $\geq 6$ . Obsessive compulsive



disorders and eating disorders were defined according to the Structured Clinical Interview for Mental Disorders (SCID 1.0)(First MB, et al, n.d.). Physical aggressiveness was also measured by the Buss-Perry Aggression Questionnaire (BPAQ) physical aggressiveness score(Buss and Perry, 1992). Sexual dysfunctions were assessed with the self-reported Sexual Functioning Questionnaire (SFQ)(Smith et al., 2002). Sleep disorders were assessed using the Pittsburgh Sleep Quality Index (PSQI)(Buysse et al., 1989) with 7 subscores (habitual sleep efficiency, sleep duration, sleep disturbances, sleep latency, subjective sleep quality, use of sleep medication, daytime dysfunction). For all these scores, higher scores indicate more severe clinical symptomatology.

### *Functioning and quality of life*

The marital status (single vs. in couple) and living autonomy (living alone vs. living with relatives or institutionalized) were reported. Daily functioning was assessed with the Global Assessment of Functioning scale (GAF) (Startup et al., 2002) and the Professional and Social Performance scale (PSP) (Morosini et al., 2000). The PSP has 4 subscores: professional functioning, social functioning, self-care and aggressiveness. In these subscores, a higher score is associated with more severe impairment, contrary to the total score in which lower score is associated with more severe impairment.

Quality of life was assessed using the SQoL-18 questionnaire, a self-administered, multidimensional instrument developed and validated for the specific assessment of QoL in SZ patients (Auquier et al., 2003; Boyer et al., 2010) with 18 items describing eight dimensions: Self-Esteem, Sentimental Life, Familial relationships, Social interactions (friend's relationships), Autonomy, Psychological Well-being, Physical Well-being, Resilience, and a total Index score (Boyer et al., 2010).

## **2.5 Statistical analysis**

Potential sources of inflammation, socio-demographics, illness characteristics, current illness severity, functioning and quality of life are presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. The data was examined for normal distribution with the Shapiro-Wilk test and for homogeneity of variance with the Levene test. Comparisons between patients with peripheral inflammation and those without regarding potential sources of inflammation, socio-demographics, illness characteristics,

current illness severity, functioning and quality of life were performed using the chi-square test for categorical variables. Continuous variables were analyzed with Student t-tests for normally distributed data and in case of normality violation, additional Mann-Whitney tests were performed to confirm the result. As detailed in the rationale, the present study was hypothesis-driven, no correction for multiple testing has been therefore carried out (Bender and Lange, 2001).

In the multivariate analyses, each variable associated with peripheral inflammation with a p value <0.05 in the univariate analyses was adjusted for sociodemographic data (age, sex and education level) in the potential sources of inflammation (table 1) and for body mass index and history of dental care in the last 12 months for illness characteristics, illness current severity (table 2), functioning and quality of life (table 3), as body mass index and history of dental care were significantly associated with peripheral inflammation. Analyses were carried out using IBM SPSS Statistics 20. All statistical tests were two-tailed, with  $\alpha$  level set at 0.05.

### 3. Results

Overall, 580 patients with a hs-CRP blood level <3 mg/L have been included in the FACE-SZ cohort, of whom 354(61%) had a blood hs-CRP level <1mg/L (no peripheral inflammation) and 226 (39%) had a [1-3[ hs-CRP blood level (peripheral inflammation). Univariate and multivariate analyses are presented in **Table 1** for socio-demographics and potential sources of inflammation, in **Table 2** for illness characteristics and current illness severity and in **Table 3** for physical health, functioning and quality of life.

#### *Potential sources of inflammation (Table 1)*

In multivariate analyses, patients with peripheral inflammation had increased weight (adjusted standardized betas; body mass index 0.216,  $p<0.001$ , abdominal perimeter 0.171,  $p<0.001$ ), less dental care during the last 12 months (aOR= 25.582,  $p=0.002$ ) increased lipid dysfunction (triglyceridemia 0.088,  $p=0.045$ ), glucose dysfunction (glycated hemoglobin 0.196,  $p=0.005$ ), and uric acid blood level (0.172,  $p<0.001$ ) compared to those without. No significant association has been found with childhood adversity, physical activity or addictions (all  $p>0.05$ ).

### *Illness characteristics and current illness severity (Table 2)*

In multivariate analyses, patients with peripheral inflammation had more severe psychotic symptomatology (adjusted betas: PANSS total score 0.218,  $p < 0.001$ , PANSS positive factor 0.150,  $p = 0.007$ ; negative factor 0.150,  $p = 0.011$ ; cognitive/disorganized factor 0.191,  $p = 0.001$ ; emotional distress factor 0.152,  $p = 0.007$ ), depressive and aggressive symptoms (Calgary depression rating scale score 0.170,  $p = 0.003$ , current major depressive disorder: adjusted odd ratios aOR= 2.212,  $p = 0.005$ , BPAQ physical aggressiveness score: 0.137,  $p = 0.025$ ).

### *Functioning and quality of life (Table 3)*

In multivariate analyses, patients with peripheral inflammation had impaired functioning (GAF score -0.142,  $p = 0.001$ ; PSP aggressiveness score: 0.166,  $p = 0.031$ ) and lower self-esteem (SQoL18 self-esteem score -0.135,  $p = 0.017$ ) compared to those without.

## **4. Discussion**

The present results confirm that patients with peripheral inflammation defined by a hs-CRP between 1 and 3 mg/L have multiple poor outcomes including more severe positive, negative, cognitive, depressive and aggressive symptomatology, impaired physical health (with increased metabolic and oxidative disorders) and impaired functioning. Overweight and lack of dental care have been identified among potential sources of inflammation.

Among potential sources of inflammation, peripheral inflammation was associated with lower dental care. Periodontitis, a major inflammatory disease of the oral mucosa, is epidemiologically associated with other chronic inflammation-driven disorders, including cardio-metabolic, neurodegenerative and autoimmune diseases and cancer (Gill et al., 2020). Of note, only 14.5% of the SZ patients reported dental care in the control group, which is much lower than the 46% of the SZ patients of a Danish study published in 2011 (Nielsen et al., 2011). Our results suggest that dental care should be a priority in physical health management in SZ outpatients. Understanding how certain extra-oral pathologies are affected by disseminated periodontal pathogens

and periodontitis-associated systemic inflammation, including adaptation of bone marrow hematopoietic progenitors, may provide new therapeutic options to reduce the risk of periodontitis-associated comorbidities(Gill et al., 2020). SZ patients are at high risk of periodontal disease due to antipsychotic medications, tobacco smoking and sugar consumption(Hu et al., 2019). The nicotine of tobacco cigarettes has anti-inflammatory properties, which may counterbalance other potential effects of tobacco smoking, which may explain the absence of significant association between peripheral inflammation and tobacco smoking(An et al., 2021).

The associations of peripheral inflammation with respectively overweight, abdominal obesity and metabolic disturbances were expected. Inflammation has been suggested to play an important role in the development and progression of metabolic syndrome(Yi et al., 2021). Dietary intake of red meat, cholesterol, saturated and trans-fatty acids and iron-containing foods is positively associated with the risk of metabolic disturbances(Firth et al., 2019). On the contrary, prebiotics consumption have been recently associated with decreased peripheral inflammatory biomarkers in a recent meta-analysis(Qu et al., 2019). Fruits and vegetables contain phytochemicals that may improve inflammation in overweight and obese patients(Poulsen et al., 2020). Diet has not been evaluated in the present study due to a lack of validated questionnaire in SZ patients. Intermittent fasting could be an interesting option for patients with peripheral inflammation. It has been recently shown to improve weight loss and to decrease abnormal inflammatory markers in a meta-analysis including 18 randomized controlled trials(Wang et al., 2020). Intermittent fasting could be an effective anti-inflammatory strategy that should be tested in patients with peripheral inflammation. Complementary agents were not captured in the FACE-SZ dataset while probiotic administration has been associated with decreased abdominal perimeter in a recent meta-analysis(Skonieczna-Żydecka et al., 2020).

We found no significant association of peripheral inflammation with childhood trauma, consistently with a previous study in a SZ population(Counotte et al., 2019). Of note, it remains unclear if childhood trauma may cause direct inflammation disturbances in adulthood in non-SZ population(Gill et al., 2020; Kuzminskaite et al., 2020). We found no association of physical activity with peripheral inflammation, however we have not distinguished some specific physical activities like high-intensity interval training that may specifically improve inflammation(Khalafi and Symonds, 2020).

The main finding of the present study is that peripheral inflammation was associated with increased positive, negative, cognitive/disorganized and depressive symptoms (for review of previous studies see(Guillaume Fond et al., 2018) and(Bora, 2019)) after adjustment for body mass index and history of dental care in the 12 previous months. We also found that peripheral inflammation was associated with increased physical aggressiveness, which is consistent with another recent study (Orsolini et al., 2018). This association was identified in our results with both self-reported (the BPAQ score) and clinician-rated scales (the PSP aggressiveness score), which strengthens our results. Using a hs-CRP cut-off of 1mg/l seem therefore relevant to address inflammation in patients with schizophrenia.

Limits and perspectives. Our analyses were hypothesis-driven, we did not therefore apply correction for multiple testing. However, these results should be considered as preliminary and should be replicated in other samples. The comparison of our results with those of previous studies should be taken with caution, as these studies included the patients with hs-CRP between 1 and 3 mg/L in their control group. This may explain some inconsistencies across studies. Socioeconomic status during childhood has not been reported, however inconsistent results have suggested a potential association with peripheral inflammation(Milaniak and Jaffee, 2019).

Strengths. The large sample of patients with a CRP blood level between 1 and 3 mg/L was possible due to the FACE-SZ cohort sample. The large number of variables and the use of standardized scales by trained psychiatrists in 10 expert centers is another strength for the present findings.

## **5. Conclusion**

The present results confirm that patients with hs-CRP level between 1 and 3 mg/L should be considered at risk for inflammation-associated disorders. Lowering weight and increasing dental care may be useful strategies to limit the sources of peripheral inflammation. Using a cut-off of 1mg/L seems therefore recommended to detect peripheral inflammation in stabilized outpatients with schizophrenia.

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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.

## References

- Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia: the Calgary Depression Scale. *Br. J. Psychiatry. Suppl.* 39–44.
- An, N., Holl, J., Wang, X., Rausch, M.A., Andrukhov, O., Rausch-Fan, X., 2021. Potential Suppressive Effect of Nicotine on the Inflammatory Response in Oral Epithelial Cells: An In Vitro Study. *Int. J. Environ. Res. Public. Health* 18. <https://doi.org/10.3390/ijerph18020483>
- Auquier, P., Simeoni, M.C., Sapin, C., Reine, G., Aghababian, V., Cramer, J., Lancon, C., 2003. Development and validation of a patient-based health-related quality of life questionnaire in schizophrenia: the S-QoL. *Schizophr. Res.* 63, 137–149.
- Bender, R., Lange, S., 2001. Adjusting for multiple testing—when and how? *J. Clin. Epidemiol.* 54, 343–349. [https://doi.org/10.1016/S0895-4356\(00\)00314-0](https://doi.org/10.1016/S0895-4356(00)00314-0)
- Bora, E., 2019. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. *Psychol. Med.* 1–9. <https://doi.org/10.1017/S0033291719001685>
- Boyer, L., Simeoni, M.-C., Loundou, A., D’Amato, T., Reine, G., Lancon, C., Auquier, P., 2010. The development of the S-QoL 18: a shortened quality of life questionnaire for patients with schizophrenia. *Schizophr. Res.* 121, 241–250.
- Buss, A.H., Perry, M., 1992. The aggression questionnaire. *J. Pers. Soc. Psychol.* 63, 452–459. <https://doi.org/10.1037//0022-3514.63.3.452>
- Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 28, 193–213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4)
- Çakici, N., van Beveren, N.J.M., Judge-Hundal, G., Koola, M.M., Sommer, I.E.C., 2019. An update on the efficacy of anti-inflammatory agents for patients with schizophrenia: a meta-analysis. *Psychol. Med.* 49, 2307–2319. <https://doi.org/10.1017/S0033291719001995>
- Counotte, J., Bergink, V., Pot-Kolder, R., Drexhage, H.A., Hoek, H.W., Veling, W., 2019. Inflammatory cytokines and growth factors were not associated with psychosis liability or childhood trauma. *PloS One* 14, e0219139. <https://doi.org/10.1371/journal.pone.0219139>
- Felger, J.C., Haroon, E., Patel, T.A., Goldsmith, D.R., Wommack, E.C., Woolwine, B.J., Le, N.-A., Feinberg, R., Tansey, M.G., Miller, A.H., 2018. What does plasma CRP tell us about peripheral and central inflammation in depression? *Mol. Psychiatry* 1–11. <https://doi.org/10.1038/s41380-018-0096-3>
- First MB, et al, n.d. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition, SCID-I/P. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
- Firth, J., Veronese, N., Cotter, J., Shivappa, N., Hebert, J.R., Ee, C., Smith, L., Stubbs, B., Jackson, S.E., Sarris, J., 2019. What Is the Role of Dietary Inflammation in Severe Mental Illness? A Review of Observational and Experimental Findings. *Front. Psychiatry* 10, 350. <https://doi.org/10.3389/fpsy.2019.00350>
- Fond, G., Berna, F., Andrianarisoa, M., Godin, O., Leboyer, M., Brunel, L., Aouizerate, B., Capdevielle, D., Chereau, I., D’Amato, T., Denizot, H., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Llorca, P.M., Mallet, J., Misdrahi, D., Passerieux, C., Richieri, R., Rey, R.,

Schandrin, A., Urbach, M., Vidailhet, P., Boyer, L., Schürhoff, F., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2017a. Chronic low-grade peripheral inflammation is associated with severe nicotine dependence in schizophrenia: results from the national multicentric FACE-SZ cohort. *Eur. Arch. Psychiatry Clin. Neurosci.* <https://doi.org/10.1007/s00406-017-0771-4>

Fond, G., Faugere, M., Richieri, R., Cermolacce, M., Korchia, T., Micoulaud-Franchi, J.A., Sunhary de Verville, P.L., Boyer, L., Lançon, C., 2021. Depressive symptoms and chronic peripheral inflammation are associated with impaired functional remission in schizophrenia independently of psychotic remission. *J. Affect. Disord.* 280, 267–271. <https://doi.org/10.1016/j.jad.2020.11.046>

Fond, G., Godin, O., Boyer, L., Berna, F., Andrianarisoa, M., Coulon, N., Brunel, L., Bulzacka, E., Aouizerate, B., Capdevielle, D., Chereau, I., D'Amato, T., Dubertret, C., Dubreucq, J., Faget, C., Leignier, S., Lançon, C., Mallet, J., Misdrahi, D., Passerieux, C., Rey, R., Schandrin, A., Urbach, M., Vidailhet, P., Llorca, P.M., Schürhoff, F., Leboyer, M., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) Group, 2018. Chronic low-grade peripheral inflammation is associated with ultra resistant schizophrenia. Results from the FACE-SZ cohort. *Eur. Arch. Psychiatry Clin. Neurosci.* <https://doi.org/10.1007/s00406-018-0908-0>

Fond, G., Godin, O., Brunel, L., Aouizerate, B., Berna, F., Bulzacka, E., Capdevielle, D., Chereau, I., Dorey, J.M., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Le Strat, Y., Micoulaud-Franchi, J.A., Misdrahi, D., Rey, R., Richieri, R., Passerieux, C., Schandrin, A., Schürhoff, F., Tronche, A.M., Urbach, M., Vidalhet, P., Llorca, P.M., Leboyer, M., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2016. Peripheral sub-inflammation is associated with antidepressant consumption in schizophrenia. Results from the multi-center FACE-SZ data set. *J. Affect. Disord.* 191, 209–215. <https://doi.org/10.1016/j.jad.2015.11.017>

Fond, G., Godin, O., Dumontaud, M., Faget, C., Schürhoff, F., Berna, F., Aouizerate, B., Capdevielle, D., Chereau, I., D'Amato, T., Dubertret, C., Dubreucq, J., Leignier, S., Mallet, J., Misdrahi, D., Passerieux, C., Rey, R., Schandrin, A., Szoke, A., Urbach, M., Vidailhet, P., Leboyer, M., Lançon, C., Boyer, L., Llorca, P.M., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2019. Sexual dysfunctions are associated with major depression, chronic inflammation and anticholinergic consumption in the real-world schizophrenia FACE-SZ national cohort. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 94, 109654. <https://doi.org/10.1016/j.pnpbp.2019.109654>

Fond, Guillaume, Lançon, C., Auquier, P., Boyer, L., 2018. C-Reactive Protein as a Peripheral Biomarker in Schizophrenia. An Updated Systematic Review. *Front. Psychiatry* 9, 392. <https://doi.org/10.3389/fpsy.2018.00392>

Fond, G., Resseguier, N., Schürhoff, F., Godin, O., Andrianarisoa, M., Brunel, L., Bulzacka, E., Aouizerate, B., Berna, F., Capdevielle, D., Chereau, I., D'Amato, T., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Lançon, C., Llorca, P.M., Mallet, J., Misdrahi, D., Passerieux, C., Rey, R., Schandrin, A., Urbach, M., Vidailhet, P., Boyer, L., Leboyer, M., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2017b. Relationships between low-grade peripheral inflammation and psychotropic drugs in schizophrenia: results from the national FACE-SZ cohort. *Eur. Arch. Psychiatry Clin. Neurosci.* <https://doi.org/10.1007/s00406-017-0847-1>

Fonseka, T.M., Müller, D.J., Kennedy, S.H., 2016. Inflammatory Cytokines and Antipsychotic-Induced Weight Gain: Review and Clinical Implications. *Mol.*



Neuropsychiatry 2, 1–14. <https://doi.org/10.1159/000441521>

Fraguas, D., Díaz-Caneja, C.M., Ayora, M., Hernández-Álvarez, F., Rodríguez-Quiroga, A., Recio, S., Leza, J.C., Arango, C., 2019. Oxidative Stress and Inflammation in First-Episode Psychosis: A Systematic Review and Meta-analysis. *Schizophr. Bull.* 45, 742–751. <https://doi.org/10.1093/schbul/sby125>

Gill, H., El-Halabi, S., Majeed, A., Gill, B., Lui, L.M.W., Mansur, R.B., Lipsitz, O., Rodrigues, N.B., Phan, L., Chen-Li, D., McIntyre, R.S., Rosenblat, J.D., 2020. The Association Between Adverse Childhood Experiences and Inflammation in Patients with Major Depressive Disorder: A Systematic Review. *J. Affect. Disord.* 272, 1–7. <https://doi.org/10.1016/j.jad.2020.03.145>

Godin, O., Leboyer, M., Schürhoff, F., Boyer, L., Andrianarisoa, M., Brunel, L., Bulzacka, E., Aouizerate, B., Berna, F., Capdevielle, D., D’Amato, T., Denizot, H., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Llorca, P.M., Mallet, J., Misdrahi, D., Passerieux, C., Rey, R., Richieri, R., Schandrin, A., Urbach, M., Vidailhet, P., Costagliola, D., Fond, G., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2017. Predictors of rapid high weight gain in schizophrenia: Longitudinal analysis of the French FACE-SZ cohort. *J. Psychiatr. Res.* 94, 62–69. <https://doi.org/10.1016/j.jpsychires.2017.06.008>

Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. *Mol. Psychiatry* 21, 1696–1709. <https://doi.org/10.1038/mp.2016.3>

Hu, K.-F., Ho, P.-S., Chou, Y.-H., Tsai, J.-H., Lin, C.-H.R., Chuang, H.-Y., 2019. Periodontal disease and effects of antipsychotic medications in patients newly diagnosed with schizophrenia: a population-based retrospective cohort. *Epidemiol. Psychiatr. Sci.* 29, e49. <https://doi.org/10.1017/S204579601900043X>

Kappelmann, N., Lewis, G., Dantzer, R., Jones, P.B., Khandaker, G.M., 2018. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol. Psychiatry* 23, 335–343. <https://doi.org/10.1038/mp.2016.167>

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.

Khalafi, M., Symonds, M.E., 2020. The impact of high-intensity interval training on inflammatory markers in metabolic disorders: A meta-analysis. *Scand. J. Med. Sci. Sports* 30, 2020–2036. <https://doi.org/10.1111/sms.13754>

Khandaker, G.M., Cousins, L., Deakin, J., Lennox, B.R., Yolken, R., Jones, P.B., 2015. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiatry* 2, 258–270. [https://doi.org/10.1016/S2215-0366\(14\)00122-9](https://doi.org/10.1016/S2215-0366(14)00122-9)

Kuzminskaite, E., Vinkers, C.H., Elzinga, B.M., Wardenaar, K.J., Giltay, E.J., Penninx, B.W.J.H., 2020. Childhood trauma and dysregulation of multiple biological stress systems in adulthood: Results from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology* 121, 104835. <https://doi.org/10.1016/j.psyneuen.2020.104835>

Leucht, S., Samara, M., Heres, S., Patel, M.X., Woods, S.W., Davis, J.M., 2014. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. *Schizophr. Bull.* 40, 314–326. <https://doi.org/10.1093/schbul/sbu001>

- Maes, M., Bocchio Chiavetto, L., Bignotti, S., Battista Tura, G., Pioli, R., Boin, F., Kenis, G., Bosmans, E., de Jongh, R., Lin, A., Racagni, G., Altamura, C.A., 2000. Effects of atypical antipsychotics on the inflammatory response system in schizophrenic patients resistant to treatment with typical neuroleptics. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* 10, 119–124.
- Marques, T.R., Ashok, A.H., Pillinger, T., Veronese, M., Turkheimer, F.E., Dazzan, P., Sommer, I.E.C., Howes, O.D., 2018. Neuroinflammation in schizophrenia: meta-analysis of in vivo microglial imaging studies. *Psychol. Med.* 1–11.  
<https://doi.org/10.1017/S0033291718003057>
- Meyer, J.M., McEvoy, J.P., Davis, V.G., Goff, D.C., Nasrallah, H.A., Davis, S.M., Hsiao, J.K., Swartz, M.S., Stroup, T.S., Lieberman, J.A., 2009. Inflammatory markers in schizophrenia: comparing antipsychotic effects in phase 1 of the clinical antipsychotic trials of intervention effectiveness study. *Biol. Psychiatry* 66, 1013–1022.  
<https://doi.org/10.1016/j.biopsych.2009.06.005>
- Milaniak, I., Jaffee, S.R., 2019. Childhood socioeconomic status and inflammation: A systematic review and meta-analysis. *Brain. Behav. Immun.* 78, 161–176.  
<https://doi.org/10.1016/j.bbi.2019.01.018>
- Misdrahi, D., Tessier, A., Daubigny, A., Meissner, W.G., Schurhoff, F., Boyer, L., Godin, O., Bulzacka, E., Aouizerate, B., Andrianarisoa, M., Berna, F., Capdevielle, D., Chereau-Boudet, I., D'Amato, T., Dubertret, C., Dubreucq, J., Faget-Agius, C., Lançon, C., Mallet, J., Passerieux, C., Rey, R., Schandrin, A., Urbach, M., Vidailhet, P., Llorca, P.-M., Fond, G., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) Group, 2019. Prevalence of and Risk Factors for Extrapyramidal Side Effects of Antipsychotics: Results From the National FACE-SZ Cohort. *J. Clin. Psychiatry* 80.  
<https://doi.org/10.4088/JCP.18m12246>
- Morosini, P.L., Magliano, L., Brambilla, L., Ugolini, S., Pioli, R., 2000. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr. Scand.* 101, 323–329.
- Nielsen, J., Munk-Jørgensen, P., Skadhede, S., Correll, C.U., 2011. Determinants of poor dental care in patients with schizophrenia: a historical, prospective database study. *J. Clin. Psychiatry* 72, 140–143. <https://doi.org/10.4088/JCP.09m05318yel>
- Orlovska-Waast, S., Köhler-Forsberg, O., Brix, S.W., Nordentoft, M., Kondziella, D., Krogh, J., Benros, M.E., 2019. Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. *Mol. Psychiatry* 24, 869–887. <https://doi.org/10.1038/s41380-018-0220-4>
- Orsolini, L., Sarchione, F., Vellante, F., Fornaro, M., Matarazzo, I., Martinotti, G., Valchera, A., Di Nicola, M., Carano, A., Di Giannantonio, M., Perna, G., Olivieri, L., De Berardis, D., 2018. Protein-C Reactive as Biomarker Predictor of Schizophrenia Phases of Illness? A Systematic Review. *Curr. Neuropharmacol.* 16, 583–606.  
<https://doi.org/10.2174/1570159X16666180119144538>
- Poulsen, N.B., Lambert, M.N.T., Jeppesen, P.B., 2020. The Effect of Plant Derived Bioactive Compounds on Inflammation: A Systematic Review and Meta-Analysis. *Mol. Nutr. Food Res.* 64, e2000473. <https://doi.org/10.1002/mnfr.202000473>
- Qu, H., Song, L., Zhang, Y., Gao, Z.-Y., Shi, D.-Z., 2019. The Effect of Prebiotic Products on

Decreasing Adiposity Parameters in Overweight and Obese Individuals: A Systematic Review and Meta-Analysis. *Curr. Med. Chem.*

<https://doi.org/10.2174/0929867327666191230110128>

Ridker Paul M, 2003. C-Reactive Protein. *Circulation* 108, e81–e85.

<https://doi.org/10.1161/01.CIR.0000093381.57779.67>

Schürhoff, F., Fond, G., Berna, F., Bulzacka, E., Godin, O., Boyer, L., Misdrahi, D., Andrianarisoa, M., Brunel, L., Coulon, N., Aouizerate, B., Capdevielle, D., Chereau, I., D'Amato, T., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Mallet, J., Rey, R., Lancon, C., Passerieux, C., Schandrin, A., Urbach, M., Vidailhet, P., Leboyer, M., Llorca, P.M., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2018. [The 10-year findings from the FondaMental Academic Center of Expertise for Schizophrenia (FACE-SZ): Review and recommendations for clinical practice]. *L'Encephale*.

<https://doi.org/10.1016/j.encep.2018.07.007>

Schürhoff, F., Fond, G., Berna, F., Bulzacka, E., Vilain, J., Capdevielle, D., Misdrahi, D., Leboyer, M., Llorca, P.-M., FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) collaborators, 2015. A National network of schizophrenia expert centres: An innovative tool to bridge the research-practice gap. *Eur. Psychiatry J. Assoc. Eur. Psychiatr.*

<https://doi.org/10.1016/j.eurpsy.2015.05.004>

Skonieczna-Żydecka, K., Kaźmierczak-Siedlecka, K., Kaczmarczyk, M., Śliwa-Dominiak, J., Maciejewska, D., Janda, K., Stachowska, E., Łoniewska, B., Malinowski, D., Borecki, K., Marlicz, W., Łoniewski, I., 2020. The Effect of Probiotics and Synbiotics on Risk Factors Associated with Cardiometabolic Diseases in Healthy People-A Systematic Review and Meta-Analysis with Meta-Regression of Randomized Controlled Trials. *J. Clin. Med.* 9.

<https://doi.org/10.3390/jcm9061788>

Smith, S.M., O'Keane, V., Murray, R., 2002. Sexual dysfunction in patients taking conventional antipsychotic medication. *Br. J. Psychiatry J. Ment. Sci.* 181, 49–55.

Startup, M., Jackson, M.C., Bendix, S., 2002. The concurrent validity of the Global Assessment of Functioning (GAF). *Br. J. Clin. Psychol.* 41, 417–422.

Wang, X., Yang, Q., Liao, Q., Li, M., Zhang, P., Santos, H.O., Kord-Varkaneh, H., Abshirini, M., 2020. Effects of intermittent fasting diets on plasma concentrations of inflammatory biomarkers: A systematic review and meta-analysis of randomized controlled trials. *Nutr. Burbank Los Angel. Cty. Calif* 79–80, 110974. <https://doi.org/10.1016/j.nut.2020.110974>

Yi, Q., Li, X., He, Y., Xia, W., Shao, J., Ye, Z., Song, P., 2021. Associations of Dietary Inflammatory Index with Metabolic Syndrome and Its Components: A Systematic Review and Meta-Analysis. *Public Health Nutr.* 1–18. <https://doi.org/10.1017/S1368980021000288>

**Table 1: Potential sources of inflammation: Univariate and multivariate models.**

Variables	Univariate model			Multivariate model	
	No inflammation N =354(61%)	Peripheral inflammation N = 226(39%)	univariate p value	standardized Beta or adjusted* odds ratio	adjusted* p value
<b>Sociodemographic variables</b>					
Age (years)	31.24(9.13)	31.65(10.15)	ns		
Sex (men)	256(72.3%)	175(77.4%)	ns		
Education level (years)	12.49(2.57)	12.01(2.73)	0.043		
<b>Childhood adversity</b>					
Childhood adversity (CTQ total score)	41.49(12.14)	42.19(11.56)	ns		
<b>Antipsychotic treatments</b>					
Second Generation Antipsychotics	263(74.3%)	170(75.2%)	ns		
First Generation Antipsychotics	57(16.1%)	48(21.2%)	ns		
Benzodiazepines	71(20.1%)	51(22.6%)	ns		
Mood stabilizers	49(13.8%)	36(15.9%)	ns		
Selective serotonin reuptake inhibitors	60(16.9%)	38(16.8%)	ns		
Norepinephrine and serotonin reuptake inhibitors	18(5.1%)	14(6.2%)	ns		

Tricyclic agents	0(0%)	2(0.9%)	ns		
Antipsychotic daily dose (CPZ-Eq, mg/day)	484.46(459.23)	586.36(606.34)	0.060	0.120	ns
<b>Physical activity</b>					
Physical activity score (min/weeks, WHO definition)	75.38(136.573)	66.98(158.679)	ns		
<b>Overweight, perivisceral fat and intestinal tract</b>					
<b>Body Mass Index (kg/m2)</b>	<b>24.37(4.09)</b>	<b>26.53(4.63)</b>	<b>&lt;0.001</b>	<b>0.216</b>	<b>&lt;0.001</b>
<b>Abdominal perimeter (cm)</b>	<b>89.93(13.70)</b>	<b>95.53(13.43)</b>	<b>&lt;0.001</b>	<b>0.171</b>	<b>&lt;0.001</b>
High Blood Pressure	49(14.6%)	28(13.4%)	ns		
HDL cholesterol (mM)	1.31(0.37)	1.26(0.37)	ns		
LDL cholesterol (mM)	2.92(0.89)	3.06(0.92)	ns		
Diagnosed diabetes	8(3.2%)	7(4.1%)	ns		
Fasting glucose (mM)	4.81(1.17)	4.97(0.98)	ns		
<b>Glycated hemoglobin (%)</b>	<b>5.18(0.37)</b>	<b>5.44(0.98)</b>	<b>0.046</b>	<b>0.196</b>	<b>0.005</b>
<b>Triglyceridemia (mM)</b>	<b>1.36(1.08)</b>	<b>1.59(1.30)</b>	<b>0.033</b>	<b>0.088</b>	<b>0.045</b>
<b>Uric acid (μmol/L)</b>	<b>290(71.76)</b>	<b>322(85.09)</b>	<b>&lt;0.001</b>	<b>0.172</b>	<b>&lt;0.001</b>
Constipation	28(15.8%)	12(14.0%)	ns		
Diarrhea	15(8.5%)	4(4.8%)	ns		
Gastrointestinal ulcer history	8(2.4%)	3(1.5%)	ns		
<b>Dental care</b>					
<b>Dental care in the last 12 months</b>	<b>35(14.5%)</b>	<b>1(0.6%)</b>	<b>&lt;0.001</b>	<b>25.582[3.438;190.347]</b>	<b>0.002</b>

<b>Addictions</b>					
Current daily tobacco smoking	171(49.9%)	120(54.8%)	ns		
Current alcohol use disorder	24(6.8%)	9(4.0%)	ns		
Current cannabis use disorder	32(9.0%)	16(8.0%)	ns		
Coffee consumption (cups/week)	116(70.3%)	60(66.7%)	ns		
<b>Inflammatory diseases</b>					
Asthma	37(10.5%)	13(5.8%)	0.045	0.648[0.328;1.281]	ns
Lupus erythematosus	1(0.3%)	0(0%)	ns		
Crohn disease	1(0.3%)	0(0%)	ns		
Psoriasis	6(1.7%)	2(0.9%)	ns		
Multiple sclerosis	1(0.3%)	1(0.4%)	ns		
Rheumatoid arthritis	0(0%)	0(0%)	-		
Any type of cancer	8(2.3%)	3(1.3%)	ns		

\* Adjusted for age, sex and education level. Ns: non significant. Significant results are in bold ( $p < 0.05$ ).

**Table 2: Illness outcomes associated with low-grade inflammation. Univariate and multivariate analyses.**

Variables	Univariate model			Multivariate model	
	No inflammation N =354(61%)	Peripheral inflammation N =	univariate p	standardized Beta or adjusted* odds	adjusted* p value

		226(39%)	value	ratio	
<b>Illness characteristics</b>					
Age at illness onset (years)	21.44(6.15)	20.45(6.54)	ns		
Age at first antipsychotic treatment (years)	22.76(6.08)	22.06(6.87)	ns		
Duration of untreated psychosis (years)	1.46(2.77)	1.58(2.97)	ns		
<b>Current illness severity / symptomatology</b>					
<b>Current psychotic severity (PANSS total score)</b>	<b>67.08(18.21)</b>	<b>76.01(20.79)</b>	<b>&lt;0.001</b>	<b>0.218</b>	<b>&lt;0.001</b>
<b>Positive factor (PANSS subscore)</b>	<b>8.86(4.20)</b>	<b>9.85(4.64)</b>	<b>&lt;0.001</b>	<b>0.150</b>	<b>0.007</b>
<b>Negative factor (PANSS subscore)</b>	<b>16.63(6.77)</b>	<b>18.49(6.47)</b>	<b>&lt;0.001</b>	<b>0.150</b>	<b>0.011</b>
<b>Cognitive / Disorganized factor (PANSS subscore)</b>	<b>7.53(3.25)</b>	<b>8.84(3.52)</b>	<b>&lt;0.001</b>	<b>0.191</b>	<b>0.001</b>
Excitement factor (PANSS subscore)	5.55(2.21)	6.19(2.48)	<0.001	0.085	ns
<b>Emotional distress factor (PANSS subscore)</b>	<b>6.82(2.97)</b>	<b>8.11(3.24)</b>	<b>&lt;0.001</b>	<b>0.152</b>	<b>0.007</b>
Extrapyramidal symptoms (Simpson&Angus scale)	0.22(0.32)	0.31(0.43)	0.019	0.062	ns
<b>Calgary Depression Rating Scale score</b>	<b>3.56(3.95)</b>	<b>5.08(4.61)</b>	<b>&lt;0.001</b>	<b>0.170</b>	<b>0.003</b>
<b>Current MDD</b>	<b>65(18.8%)</b>	<b>66(31.4%)</b>	<b>0.001</b>	<b>2.212 [1.275;3.831]</b>	<b>0.005</b>
Current obsessive-compulsive disorder	31(9.4%)	10(5.0%)	0.061	0.524[0.216;1.270]	ns

Current eating disorder	22(7.1%)	7(3.6%)	ns		
<b>Physical aggressiveness (BPAQ score)</b>	<b>19.10(7.66)</b>	<b>21.5(7.88)</b>	<b>0.001</b>	<b>0.137</b>	<b>0.025</b>
Sexual dysfunction (SFQ score)	24(39.3%)	11(33.3%)	ns		
Sleep efficiency (PSQI subscore)	25(16.2%)	10(12.8%)	ns		
Sleep duration (PSQI subscore)	12(7.8%)	3(3.8%)	ns		
Sleep disturbances (PSQI subscore)	52(31.5%)	28(35.4%)	ns		
Sleep latency (PSQI subscore)	77(47.0%)	40(50.0%)	ns		
Poor subjective sleep quality (PSQI subscore)	34(20.6%)	21(26.6%)	ns		
Use of sleep medication (PSQI subscore)	48(29.1%)	25(31.6%)	ns		
Daytime dysfunction (PSQI subscore)	58(35.2%)	41(51.9%)	0.013	1.639 [0.759;3.538]	ns
Any sleep disorder (Total PSQI score)	89(57.8%)	52(67.5%)	ns		

\* Adjusted for body mass index and dental care in the last 12 months. Ns: non significant. Significant results are in bold (p<0.05).

BPAQ : Buss-Perry Aggression Questionnaire ; hs-CRP : highly sensitive - C reactive protein ; MDD: major depressive disorder; MARS : Medication Adherence Rating Scale ; PANSS : Positive and Negative Syndrome Scale ; SAS : Simpson-Angus Scale ; WHO: World Health Organization, YMRS : Young Mania Rating Scale.



**Table 3: Functioning and quality of life outcomes associated with low-grade inflammation. Univariate and multivariate analyses.**

Variables	Univariate model			Multivariate model	
	No inflammation N =354(61%)	Peripheral inflammation N = 226(39%)	univariate p value	standardized Beta or adjusted* odds ratio	adjusted* p value
<b>Professional and social Functioning</b>					
Single	276(90.2%)	193(93.7%)	ns		
Living alone	120(39.3%)	70(33.8%)	ns		
<b>GAF score</b>	<b>50.87(12.97)</b>	<b>47.48(12.82)</b>	<b>0.003</b>	<b>-0.142</b>	<b>0.001</b>
PSP professional functioning**	0.69(0.46)	0.83(0.38)	0.010	0.046	ns
PSP social functioning**	0.71(0.46)	0.83(0.38)	0.014	0.120	ns
PSP self-neglect**	0.19(0.39)	0.30(0.46)	0.025	0.110	ns
<b>PSP aggressiveness**</b>	<b>0.03(0.18)</b>	<b>0.13(0.34)</b>	<b>0.010</b>	<b>0.166</b>	<b>0.031</b>
<b>PSP total functioning score</b>	<b>56.61(14.75)</b>	<b>47.76(16.72)</b>	<b>&lt;0.001</b>	<b>-0.192</b>	<b>0.011</b>
<b>Quality of life</b>					
<b>Self-esteem</b>	<b>51.11(29.18)</b>	<b>42.99(30.44)</b>	<b>0.002</b>	<b>-0.135</b>	<b>0.017</b>
Sentimental life	35.45(30.06)	32.87(30.53)	ns		
Familial relationship	70.26(25.16)	70.25(26.80)	ns		
Social interaction	50.26(27.55)	44.62(31.66)	0.028	-0.095	ns
Autonomy	60.87(26.32)	56.93(28.49)	ns		
Psychological well-being	54.57(26.46)	44.62(31.66)	ns		
Physical well-being	47.49(27.55)	45.21(28.55)	ns		

Resilience	56.28(26.93)	52.28(27.22)	ns		
SQoL total Index	53.28(17.92)	49.65(19.07)	0.024	-0.090	ns

\* Adjusted for body mass index and dental care in the past 12 months. Ns: non significant. Significant results are in bold (p<0.05).

\*\* higher scores are associated with lower functioning