Inflammatory Markers in Patients With Treatment-Resistant Schizophrenia in Ethiopia: A Comparative Study

Feyissa Challa

Ethiopian Public Health Institute

Daniel Seifu

Addis Ababa University

Meron Seleshi

Ethiopian Public Health Institute

Tigist Getahun

Ethiopian Public Health Institute

Desta Kassa

Ethiopian Public Health Institute

Melkam Alemayehu

Addis Ababa University

Miraf Mesfin

Addis Ababa University

Yimtubezinash Woldeamanuel (✉ yimtuwa@gmail.com)

Addis Ababa University

Abebaw Fekadu

Addis Ababa University

Zelege Geto

Ethiopian Public Health Institute

Research Article

Keywords: schizophrenia, Interleukin-6 (IL-6), high sensitive C - reactive protein (hsCRP), Inflammatory markers, Ethiopia.

Posted Date: January 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-138829/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Accumulating evidence indicates that schizophrenia is accompanied by an activation of the immune system; however, there is limited data from low and middle-income countries. Inflammatory markers could even be more important in these settings where infectious conditions may play a more prominent role in the causation and maintenance of schizophrenia. The aim of this study was to assess the level of inflammatory markers–High sensitive C-reactive protein (hsCRP) and Interleukin-6 (IL-6)–in patients with schizophrenia.

Materials and methods: The study population consisted of a total of 132 study participants; 82 with schizophrenia and 50 controls. hsCRP and IL-6 were measured using Cobas Intgera 400 Plus and Cobas e 411 analysers respectively.

Results: The levels of hsCRP and IL-6 were significantly increased among patients with schizophrenia compared to controls. Controlling for potential confounders (age, sex and body mass index), having a diagnosis of schizophrenia remained significantly associated with increased hsCRP (beta =0.29; 95% CI=0.10, 0.49) and IL-6 (beta=3.60; 95% CI: 1.35, 5.86).

Conclusion: The finding is consistent with reports from high income countries and confirms that inflammatory processes may have a role in the pathophysiology of schizophrenia regardless of setting. Despite failure of some interventions with anti-inflammatory properties, interventions to reduce inflammation are still worth pursuing.

Background

Schizophrenia is a relatively rare but serious mental disorder affecting about 1% of the adult population. Due to medical co-morbidities and other patient and service factors, people diagnosed with schizophrenia have a high overall mortality rate [1, 2], which may occur 20 to 30 years earlier than the general population [3]. The exact cause of schizophrenia is not established; however, epidemiological evidence indicates that several risk factors, including genetic susceptibility[4], season of birth[5], increasing parental age[6], and prenatal exposure to infection[7] may contribute to the development of schizophrenia.

Immunological dysfunction and inflammation, and exposure to infectious agents that lead to immune response, such as *Toxoplasma gondii*[8], influenza [9] and interaction of environmental factors and stress are also considered important[10]. This theory has been supported by finding of elevated C-reactive Protein (CRP) and interleukin 6 (IL-6) in mental disorders[11].

CRP is nonspecific serum protein, traditionally considered as an acute phase immune response marker. It is mainly produced by liver cells and is directly modulated by both interleukin (IL) 1 β and IL-6, both inflammatory markers increased during psychotic state[12–14].

A number of studies in both first episode and persistent or recurrent schizophrenia show increased serum levels of acute phase proteins, such as CRP, and proinflammatory markers like tumor necrosis factor (TNF- α), IL-6, and IL-1 β , although with some inconsistency[15–18]. A recent meta-analysis reported higher CRP levels in patients with schizophrenia than control groups [13] and two individual studies (case-control and longitudinal birth cohort study) indicated that increased CRP was associated with increased risk of schizophrenia [19, 20]. Yet, other studies, albeit fewer, have found no difference between the level of serum CRP or IL-6 in patients with schizophrenia and control subjects[21, 22].

Most of these studies have been conducted in high income countries. Although infectious causes may have more relevance in the causation of schizophrenia in low and middle-income countries, there is extreme dearth of data from these countries. Therefore, this study aimed to investigate the serum level of inflammatory markers (CRP and IL-6) among patients with schizophrenia.

Results

Demographic and Clinical Characteristics

The socio-demographic characteristics of participants is presented in Table 1. Compared to the control group, participants with schizophrenia were predominantly male and slightly older. Over two-thirds of the patients with schizophrenia were single during study period, and lived with parental family. Patients with Schizophrenia and control participants were similar in terms of current BMI. The mean PANSS score was 89.2 and over 61% had markedly ill as defined by their PANSS score.

Table 1.
Demographic and clinical Characteristics of study participants

Characteristics	Cases (Patients with Schizophrenia, n = 82)	Healthy Control Subjects (n = 50)
Males/Females (n)	79 / 3	23 / 27
Age, Years Mean (SD)	35.1 (9.7)	28.8 (9.9)
BMI Mean (SD)	21.0 (3.35)	22.0 (2.8)
Ethnicity n (%)		
Oromo	11 (13.4)	n/a
Amhara	13 (15.9)	n/a
Tigray	8(9.8)	n/a
Gurage	45 (54.9)	n/a
Others	5(6.1)	n/a
Marital status n (%)		
Single	67(81.7)	n/a
Married	6(7.3)	n/a
Divorced	4(4.9)	n/a
Widowed	5(6.1)	n/a
Cohabiting	0	n/a
Living arrangement n (%)		
Lives alone	3 (3.7)	n/a
Lives with Parental family	63(76.8)	n/a
Lives with Marital family	6(7.3)	n/a
Lives with other relatives	10 (12.2)	n/a
Lives with friends	0	n/a
Age of onset in Years, Mean (SD)	22.88 (6.63)	n/a
PANSS total score Mean (SD)	89.2 (20.2)	n/a

*BMI = Body mass index, SD = Standard deviation,
n/a= Not Available*

Characteristics	Cases (Patients with Schizophrenia, n = 82)	Healthy Control Subjects (n = 50)
PANSS classification in n (%)		
Markedly ill	50 (61.0)	n/a
Severely ill	22(26.8)	n/a
Extreme severely ill	10(12.2)	n/a
Duration of current episode		n/a
In months Mean (SD)	13.82(18.2)	
Current Episode (%)		
First Episode	4.9	n/a
Relapse Episode	95.1	n/a
Smoking Status Yes/No	15/67	n/a
<i>BMI = Body mass index, SD = Standard deviation, n/a= Not Available</i>		

Immunological findings

Forty nine percent and 43% of patients with schizophrenia had elevated hsCRP and IL-6 values respectively. Similarly, the mean value of hsCRP and IL-6 was higher compared in cases compared with that of controls (2.87 mg/L, and 6.63 pg/ml among patients with schizophrenia and 0.67 mg/L and 3.37 pg/ml among controls group (Fig. 1.)) HsCRP level was statistically significantly associated with having a diagnosis of schizophrenia in both the crude ($\beta = 0.37$, 95% CI = 0.20, 0.54, $P < 0.001$) and the adjusted ($\beta = 0.29$, 95% CI = 0.10, 0.49, $P = 0.003$) models. Serum IL-6 was also higher among patients with schizophrenia in both the crude ($\beta = 2.86$, 95% CI = 1.11, 4.62, $P = 0.001$) and the adjusted ($\beta 3.60$ 95% CI: 1.35, 5.86 $p = 0.002$) models (Tables 2 and 3).

Table 2.
Comparison of the inflammatory markers (hsCRP, IL-6) between cases (participants with schizophrenia) and the control group

Marker Variables		Schizophrenia n (%)	Control group n (%)	χ^2	df	p-value
hsCRP	Normal	42(51.2)	42(84.0)	14.423	1	< 0.001
	Elevated ^Φ	40(48.8)	8 (16.0)			
IL-6	Normal	47(57.3)	40 (80)	7.113	1	0.008
	Elevated ^Δ	35(42.7)	10(20)			

^ΦhsCRP values of > 1 mg/L were considered elevated

^ΔIL-6 values > 7 pg/ml were considered elevated

Other factors associated with hsCRP in the adjusted model were age and BMI (Table 3)

Table 3.
Factors associated with serum level of hsCRP

Factors	Unadjusted hsCRP (log Transformed)	adjusted* hsCRP (log transformed)
	β 95% CI P	β 95% CI P
Group Schizophrenia	0.37 0.20 0.54 <0.001	0.29 0.10 0.49 0.003
Control	Ref.	
Gender Male	0.21 0.01 0.42 0.041	0.15 -1.08 0.38 0.206
Female	Ref.	
Age 18–24 years	-0.45 -0.72 -0.17 0.001	-0.40 -0.66 -0.14 0.003
25–34 years	-0.23 -0.48 0.02 0.076	-0.26 -0.49 -0.03 0.028
35–44 years	-0.14 -0.42 0.14 0.313	-0.24 -0.48 0.01 0.062
45+ years	Ref	
BMI Underweight	-0.53 -0.86 -0.21 0.001	-0.71.. -1.02 -0.41 <0.001
Normal	-0.40 -0.67 -0.13 0.004	-0.40 -0.65 -0.15 0.002
Overweight/Obese	Ref	

There were no associations between IL-6 and age of onset, duration of current episode, and total PANSS score and smoking status. Similarly, there were no associations between hsCRP and age of onset, duration of current episode, and smoking status. However, there was significant albeit negative association between PANSS score and hsCRP (β =-0.01; 95% CI= -0.02, -0.03; p = 0.007). (Tables 4 and 5)

Table 4.
Factors associated with serum level of IL-6

Factors	unadjusted IL-6	adjusted * IL-6
	β 95% CI P	β 95% CI P
Schizophrenia	2.86 1.11 4.62 0.001	3.60 1.35 5.86 0.002
Control	Ref.	
Gender	1.16 -0.94 3.26 0.280	-0.92 -3.52 1.68 0.489
Male	Ref.	
Female		
Age	-1.75 -4.67 1.17 0.241	-0.97 -3.95 2.01 0.524
18–24 years	-1.00 -3.71 1.72 0.471	-0.76 -3.40 1.89 0.575
25–34 years	-1.46 -4.42 1.50 0.332	-1.76 -4.62 1.10 0.227
35–44 years	Ref.	
45 + years		
BMI	-0.58 -4.04 2.89 0.744	-1.20 -4.69 2.30 0.503
Underweight	0.27 -2.63 3.17 0.855	0.38 -2.50 3.26 0.797
Normal Overweight/Obese	Ref.	

Table 5
Associations between Clinical Characteristics of schizophrenia and inflammatory markers (hsCRP and IL-6).

Factors	IL-6	hsCRP log transformed
	β 95% CI P	β 95% CI P
Age of onset of illness(Months)	0.02 -0.18 0.22 0.840	0.03 -0.02 0.02 0.783
Duration of current episode(Month)	0.02 -0.05 0.09 0.613	-0.0 -0.08 0.01 0.868
Duration of illness	-0.04 -0.20 0.13 0.673	0.014 0.00 0.028 0.058
PANSS	0.012 -0.01 0.09 0.776	-0.11 -0.02 -0.04 0.003
Smoking	0.05 -0.23 0.33 0.730	0.06 -0.24 0.37 0.695

Discussion

The main finding of the study is that significantly higher level of both hsCRP and IL-6 were observed in patients with schizophrenia than the control group. To the best of our knowledge, this is the first study to investigate the serum level of both hsCRP and IL-6 among patients with schizophrenia in Ethiopia. It is also one of the very few studies from Africa. More broadly, diagnosis of inflammatory diseases and inflammatory markers in Africa is rare. Nevertheless, there is evidence of increase in the incidence and prevalence of some inflammatory diseases in the developing world, which may increase the significance of inflammation in neuropsychiatric syndromes.

The result of the present study concurs with studies from Western countries that consistently indicate that patients with schizophrenia have high serum levels of hsCRP and IL-6[19, 23–27]. Elevated inflammatory markers in patients with schizophrenia have been reported in case control studies[19, 28] and treatment studies[29]. This is also found in people with both acute[24], chronic [25] and treatment-resistant[30] illnesses. Because of the consistency of this finding, neuro-inflammation has been linked with the causation of schizophrenia and other mental disorders. However, such studies are rare in low and middle income countries where the majority of the population of the world lives. We believe that this study contributes to this particular knowledge gap and the broader issue of lack of such studies even in the general population[31].

A significant negative correlation was observed between hsCRP and total PANSS score in our study. The result in the literature in this regard is mixed: some studies have reported negative correlation as observed in our study[32] while others have reported either positive association[28, 33] or no association between hsCRP and total PANSS score[34–37]. Despite these inconsistencies, hsCRP appears to be an important inflammatory marker in our particular setting although additional confirmatory studies would be needed.

The pathophysiology of schizophrenia has been linked with chronic inflammation, which stimulates inflammatory markers like CRP and IL-6[38]. Both CRP and IL-6 have important roles in the inflammatory processes and CRP has been widely considered as a state marker along with other cytokines like TNF- α . CRP is an acute phase protein and produced by hepatocyte cell when stimulated by inflammatory markers including IL-6. Under normal conditions, CRP doesn't cross the blood-brain barrier. Increasing serum level of CRP may increase the permeability of blood-brain barrier by affecting the function of tight junction which facilitates the entry of pro-inflammatory cytokines and CRP itself into the central nervous system. This would support the potential role of CRP in the pathophysiology of schizophrenia. Moreover, studies based on cell culture indicate that CRP can induce a pro-inflammatory state in microglia, thus suggesting that CRP may be linked to neuro-inflammation in the central nervous system[39–41].

Conclusion

To the best of our knowledge, this is the first study that compares the inflammatory markers of patients with treatment resistant schizophrenia with a control group. The result suggests that there is a higher level of hsCRP and IL-6 in patients with schizophrenia compared to their control groups. While the cross-sectional design and relatively small sample size are potential limitations of this study, taken together

with findings from developed countries, underscore the fact that inflammation plays an important role in the pathogenesis of schizophrenia globally.

Methods

Participants

Eighty-two patients with Schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders Fourth edition (DSM-IV)[42] were recruited from Amanuel Specialized Mental Hospital, the main national institution for the care of those with severe mental illness in the country, between January 2015 and March 2016. Participants were recruited as part of a clinical trial, the MINOS (MINOcycline for Schizophrenia) Trial[43] (Clinicaltrials.gov identifier: NCT01809158) and were at least 18 years of age with a confirmed diagnosis of schizophrenia using standardized evaluation (Operational Criteria for Research-OPCRIT) administered by a psychiatrist and a recent onset of illness (duration under five years). They had at least moderately severe illness with a Positive and Negative Syndrome Scale score of 75 or more and have been on antipsychotic treatment for at least four weeks with little response. They had no gross physical or neurological co-morbidity and substance abuse. Because of the nature of the trial, women of child bearing age were excluded. For this study on inflammatory markers, the first 82 participants who provided blood sample were included. Fifty healthy control subjects were recruited in the same geographic area as summarized in Table 1. The full medical history of study participants were evaluated to exclude any existing systemic diseases that may affect the parameters of inflammatory markers, and all had no detected medical illness.

Assessments

A demographic questionnaire that included age, sex, and body mass index (BMI) was completed by trained Clinical Nurse. Obesity estimations were made from the BMI: Underweight (< 18.50), Normal (18.5-24.99), Overweight and Obese (25 and above). The severity of the symptoms of schizophrenia was assessed with the PANSS, a widely used semi-structured instrument in schizophrenia research. The Total PANSS score was used in this study. The PANSS has been used successfully in a clinical trial in Ethiopia[44]

Serum IL-6 and hsCRP measurement

Experienced phlebotomists collected 4–5 ml of blood from both study participants and controls after 8–10 hours of overnight fasting. Centrifugation was done at 5000 rpm on clotted blood for 10 minutes, and aliquots were stored at -80°C until analysis performed at the Clinical Chemistry laboratory of the Ethiopia Public Health Institute. Both hsCRP levels and IL-6 were measured by turbidimetric and Electrochemiluminescence immunoassay method using Cobas Integra 400 Plus and Cobas e411 (Roche Diagnostics GmbH, Mannheim, Germany) respectively. The lowest detectable limit for hsCRP was

0.1 mg/L and for IL6 was 1.0 pg/ml. IL-6 values of > 7 pg/ml were considered high while the corresponding value for hsCRP was > 1 mg/L.

Statistical analysis

Statistical analyses were done using SPSS Version 22.00 (SPSS Inc. Chicago, IL, USA). Simple descriptive and comparative analyses were carried out initially. For more advanced analysis, linear regression was used after evaluating the normality of the distribution of both hsCRP and IL-6. hsCRP was not normally distributed and thus was log-transformed. Gender, age, and BMI, factors previously reported to be associated with hsCRP and IL-6, were considered confounders and adjusted for in the linear regression model. All value of $p < 0.05$ were considered significant.

Abbreviations

hsCRP

High sensitive C-reactive protein, IL-6:Interleukin-6, CRP:C-reactive Protein, TNF:tumor necrosis factor, DSM-IV:Diagnostic and Statistical Manual of Mental Disorders Fourth edition, IRB; Institutional Review Board, BMI:body mass index

Declarations

Ethical approval and consent to participate

Ethical Clearance was obtained from the Institutional Review Board (IRB) of Addis Ababa University, College of Health Sciences (Protocol number: 062/11/Psy) and the National Research Ethics Review Committee (Ref. No: 3.10/670/04). Written informed consent was obtained from each participant after detailed explanation of the objectives of the study, risk, and benefits. Guardians or next of kins' informed consent was obtained for those individuals that do not have the capacity to consent. All methods were carried out in accordance with the Declaration of Helsinki.

Consent for publications

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the first author Feyissa Challa on reasonable request.

Competing Interests

The authors declare no conflict of interest.

Funding

This study was funded by The Stanley Medical Research Institute (SMRI).

Authors' contributions

FC and AF were the principal investigators of the study. FC, AF, and YW took the leading role from conception, design, and supervising the data collection process up to the final analysis and preparation of the manuscript. DS and DK participated in reviewing the method part and provided critical comments. MA contributed to the writing of the manuscript. MM and MA coordinated the project and were responsible for the data acquisitions. MS and TG contributed to the methodology and laboratory analysis. All authors read and approved the final manuscript.

Acknowledgments

We gratefully acknowledge the financial support of the Stanley Medical Research Institute (SMRI), which supported the MINOS trial and the Ethiopian Public Health Institute, National References for Clinical Chemistry for supporting the laboratory analysis by providing finances and facility.

References

1. Chaikunapruk N, Chong HY, Teoh SL, Wu DB-C, Kotirum S, Chiou C-F: **Global economic burden of schizophrenia: a systematic review.** *NDT* 2016:357.
2. Saha S, Chant D, Welham J, McGrath J: **A Systematic Review of the Prevalence of Schizophrenia.** *PLoS Med* 2005, **2**(5):e141.
3. Fekadu A, Medhin G, Kebede D, Alem A, Cleare AJ, Prince M, Hanlon C, Shibre T: **Excess mortality in severe mental illness: 10-year population-based cohort study in rural Ethiopia.** *British Journal of Psychiatry* 2015, **206**(4):289–296.
4. Allen NC, Bagade S, McQueen MB, Ioannidis JPA, Kavvoura FK, Khoury MJ, Tanzi RE, Bertram L: **Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database.** *Nat Genet* 2008, **40**(7):827–834.
5. Messias E, Kirkpatrick B, Bromet E, Ross D, Buchanan RW, Carpenter WT, Tek C, Kendler KS, Walsh D, Dolfus S: **Summer Birth and Deficit Schizophrenia: A Pooled Analysis From 6 Countries.** *Arch Gen Psychiatry* 2004, **61**(10):985.
6. Sipos A, Rasmussen F, Harrison G, Tynelius P, Lewis G, Leon DA, Gunnell D: **Paternal age and schizophrenia: a population based cohort study.** *BMJ* 2004, **329**(7474):1070.
7. Kneeland RE, Fatemi SH: **Viral infection, inflammation and schizophrenia.** *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2013, **42**:35–48.
8. Khademvatan S, Saki J, Khajeddin N, Izadi-Mazidi S, Beladi R, Shafiee B, Salehi Z: **Toxoplasma gondii Exposure and the Risk of Schizophrenia.** *Jundishapur J Microbiol* 2014, **7**(9).
9. Limosin F, Rouillon F, Payan C, Cohen JM, Strub N: **Prenatal exposure to influenza as a risk factor for adult schizophrenia.** *Acta Psychiatr Scand* 2003, **107**(5):331–335.

10. Howes OD, McCutcheon R: **Inflammation and the neural diathesis-stress hypothesis of schizophrenia: a reconceptualization.** *Transl Psychiatry* 2017, **7**(2):e1024-e1024.
11. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB: **Association of Serum Interleukin 6 and C-Reactive Protein in Childhood With Depression and Psychosis in Young Adult Life: A Population-Based Longitudinal Study.** *JAMA Psychiatry* 2014, **71**(10):1121.
12. Singh B, Chaudhuri TK: **Role of C-reactive protein in schizophrenia: An overview.** *Psychiatry Research* 2014, **216**(2):277–285.
13. Miller BJ, Culpepper N, Rapaport MH: **C-Reactive Protein Levels in Schizophrenia: A Review and Meta-Analysis.** *Clinical Schizophrenia & Related Psychoses* 2014, **7**(4):223–230.
14. Joseph J, Depp C, Martin AS, Daly RE, Glorioso DK, Palmer BW, Jeste DV: **Associations of high sensitivity C-reactive protein levels in schizophrenia and comparison groups.** *Schizophrenia Research* 2015, **168**(1–2):456–460.
15. Barzilay R, Lobel T, Krivoy A, Shlosberg D, Weizman A, Katz N: **Elevated C-reactive protein levels in schizophrenia inpatients is associated with aggressive behavior.** *European Psychiatry* 2016, **31**:8–12.
16. Hope S, Hoseth E, Dieset I, Mørch RH, Aas M, Aukrust P, Djurovic S, Melle I, Ueland T, Agartz I *et al*: **Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls.** *Schizophrenia Research* 2015, **165**(2–3):188–194.
17. Fan X, Pristach C, Liu EY, Freudenreich O, Henderson DC, Goff DC: **Elevated serum levels of C-reactive protein are associated with more severe psychopathology in a subgroup of patients with schizophrenia.** *Psychiatry Research* 2007, **149**(1–3):267–271.
18. Horsdal HT, Wimberley T, Benros ME, Gasse C: **C-reactive protein levels and treatment resistance in schizophrenia-A Danish population-based cohort study.** *Hum Psychopharmacol Clin Exp* 2017, **32**(6):e2632.
19. Inoshita M, Numata S, Tajima A, Kinoshita M, Umehara H, Nakataki M, Ikeda M, Maruyama S, Yamamori H, Kanazawa T *et al*: **A significant causal association between C-reactive protein levels and schizophrenia.** *Sci Rep* 2016, **6**(1):26105.
20. Metcalf SA, Jones PB, Nordstrom T, Timonen M, Mäki P, Miettunen J, Jääskeläinen E, Järvelin M-R, Stochl J, Murray GK *et al*: **Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: A prospective birth cohort study.** *Brain, Behavior, and Immunity* 2017, **59**:253–259.
21. Hope S, Melle I, Aukrust P, Steen NE, Birkenaes AB, Lorentzen S, Agartz I, Ueland T, Andreassen OA: **Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor.** *Bipolar Disorders* 2009, **11**(7):726–734.
22. Fernandez-Egea E, Bernardo M, Donner T, Conget I, Parellada E, Justicia A, Esmatjes E, Garcia-Rizo C, Kirkpatrick B: **Metabolic profile of antipsychotic-naïve individuals with non-affective psychosis.** *British Journal of Psychiatry* 2009, **194**(5):434–438.
23. Akanji AO, Ohaeri JU, Al-Shammri S, Fatania HR: **Association of blood levels of C-reactive protein with clinical phenotypes in Arab schizophrenic patients.** *Psychiatry Research* 2009, **169**(1):56–61.

24. Lin CC, Chang CM, Chang PY, Huang TL: **Increased interleukin-6 level in Taiwanese schizophrenic patients.** *Chang Gung medical journal* 2011, **34**(4):375–381.
25. Luo Y, He H, Zhang M, Huang X, Zhang J, Zhou Y, Liu X, Fan N: **Elevated serum levels of TNF- α , IL-6 and IL-18 in chronic schizophrenic patients.** *Schizophrenia Research* 2014, **159**(2–3):556–557.
26. Canetta S, Sourander A, Surcel H-M, Hinkka-Yli-Salomäki S, Leiviskä J, Kellendonk C, McKeague IW, Brown AS: **Elevated Maternal C-Reactive Protein and Increased Risk of Schizophrenia in a National Birth Cohort.** *AJP* 2014, **171**(9):960–968.
27. Dunjic-Kostic B, Pantovic-Stefanovic M, Ivkovic M, Damjanovic A, Lackovic M, Jasovic-Gasic M: **Schizophrenia and cytokines.** *Engrami* 2015, **37**(1):55–61.
28. Fawzi MH, Fawzi MM, Fawzi MM, Said NS: **C-reactive protein serum level in drug-free male Egyptian patients with schizophrenia.** *Psychiatry Research* 2011, **190**(1):91–97.
29. Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, Nardin P, Gonçalves CA, Berk M: **C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications.** *Mol Psychiatry* 2016, **21**(4):554–564.
30. Klemettilä J-P, Kampman O, Seppälä N, Viikki M, Hämäläinen M, Moilanen E, Leinonen E: **Cytokine and adipokine alterations in patients with schizophrenia treated with clozapine.** *Psychiatry Research* 2014, **218**(3):277–283.
31. Kohler IV, Soldo BJ, Anglewicz P, Chilima B, Kohler H-P: **Association of blood lipids, creatinine, albumin, and CRP with socioeconomic status in Malawi.** *Popul Health Metrics* 2013, **11**(1):4.
32. Zhang Q, Hong W, Li H, Peng F, Wang F, Li N, Xiang H, Zhang Z, Su Y, Huang Y *et al*: **Increased ratio of high sensitivity C-reactive protein to interleukin-10 as a potential peripheral biomarker of schizophrenia and aggression.** *International Journal of Psychophysiology* 2017, **114**:9–15.
33. Wium-Andersen MK, Ørsted DD, Nordestgaard BG: **Elevated C-Reactive Protein Associated With Late- and Very-Late-Onset Schizophrenia in the General Population: A Prospective Study.** *Schizophrenia Bulletin* 2014, **40**(5):1117–1127.
34. Boozalis T, Teixeira AL, Cho RY-J, Okusaga O: **C-Reactive Protein Correlates with Negative Symptoms in Patients with Schizophrenia.** *Front Public Health* 2018, **5**:360.
35. Devanarayanan S, Nandeeshha H, Kattimani S, Sarkar S, Jose J: **Elevated copper, hs C-reactive protein and dyslipidemia in drug free schizophrenia: Relation with psychopathology score.** *Asian Journal of Psychiatry* 2016, **24**:99–102.
36. Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R: **C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia.** *Schizophrenia Research* 2007, **93**(1–3):261–265.
37. Johnsen E, Fathian F, Kroken RA, Steen VM, Jørgensen HA, Gjestad R, Løberg E-M: **The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis.** *BMC Psychiatry* 2016, **16**(1):60.
38. Fond G, Berna F, Andrianarisoa M, Godin O, Leboyer M, Brunel L, Aouizerate B, Capdevielle D, Chereau I, D'Amato T *et al*: **Chronic low-grade peripheral inflammation is associated with severe nicotine**

- dependence in schizophrenia: results from the national multicentric FACE-SZ cohort.** *European archives of psychiatry and clinical neuroscience* 2017, **267**(5):465–472.
39. Adami C, Sorci G, Blasi E, Agneletti AL, Bistoni F, Donato R: **S100B expression in and effects on microglia.** *Glia* 2001, **33**(2):131–142.
40. Uranova NA, Zimina IS, Vikhreva OV, Krukov NO, Rachmanova VI, Orlovskaya DD: **Ultrastructural damage of capillaries in the neocortex in schizophrenia.** *The world journal of biological psychiatry: the official journal of the World Federation of Societies of Biological Psychiatry* 2010, **11**(3):567–578.
41. Najjar S, Pearlman DM, Devinsky O, Najjar A, Zagzag D: **Neurovascular unit dysfunction with blood-brain barrier hyperpermeability contributes to major depressive disorder: a review of clinical and experimental evidence.** *Journal of neuroinflammation* 2013, **10**:142.
42. Association. AP: **Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).** *Diagnostic Stat Man Ment Disord* 2013.
43. Fekadu A, Mesfin M, Medhin G, Alem A, Teferra S, Gebre-Eyesus T, Seboxa T, Assefa A, Hussein J, Lemma MT *et al*: **Adjuvant therapy with minocycline for schizophrenia (The MINOS Trial): study protocol for a double-blind randomized placebo-controlled trial.** *Trials* 2013, **14**(1):406.
44. Shibre T, Alem A, Abdulahi A, Araya M, Beyero T, Medhin G, Deyassa N, Negash A, Nigatu A, Kebede D *et al*: **Trimethoprim as Adjuvant Treatment in Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial.** *Schizophrenia Bulletin* 2010, **36**(4):846–851.

Figures

Figure 1

Mean serum level of hsCRP and IL-6 in schizophrenia and control group. P values derived after adjustment for gender, age, and BMI