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Authors

Kelsven, Skylar
de la Fuente-Sandoval, Camilo
Achim, Cristian L
et al.

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Immuno-Inflammatory Changes Across Phases of Early Psychosis: The Impact of Antipsychotic Medication and Stage of Illness

Skylar Kelsven, M.S.[1], **Camilo de la Fuente-Sandoval, M.D., Ph.D.**[2,3], **Cristian L. Achim, M.D., Ph.D.**[4], **Francisco Reyes-Madrigal, M.D., M.Sc.**[2], **Heline Mirzakhanian, Ph.D.**[4], **Isabel Domingues, M.D.**[4], **Kristin Cadenhead, M.D.**[4]

[1]San Diego State University/ University of California, San Diego, Joint Doctoral Program in Clinical Psychology San Diego, CA, United States

[2]Laboratory of Experimental Psychiatry, Instituto Nacional de Neurología y Neurocirugía (INNN), Mexico City, Mexico

[3]Neuropsychiatry Department, INNN, Mexico City, Mexico

[4]Department of Psychiatry, University of California San Diego, La Jolla, CA, United States

Abstract

Introduction.—Research examining the role of inflammation in psychosis has produced inconsistent results. Variables that influence inflammation, including antipsychotic medication, are inconsistently controlled across studies and variation of inflammatory analytes across stages of psychosis may also influence findings. The purpose of this study was to assess for evidence of immuno-inflammatory dysregulation across the stages of early psychosis. We examined a immuno-inflammatory anayltes in subjects at clinical high risk (CHR) for developing a psychotic disorder, antipsychotic-naïve (-n) and antipsychotic treated (-a)subjects in their first episode of psychosis (FEP), and healthy control (HC) subjects.

Methods.—A total of 11 subjects at CHR, 50 subjects within their FEP (40 FEP-n, 10 FEP-a), and 10 HC subjects were recruited from early psychosis programs in San Diego and Mexico City. Plasma was collected for biomarker assay.

Results.—Immuno-inflammatory analytes significantly differed between groups: Interferon-gamma (IFN-γ), Interleukin-10 (IL-10), Eotaxin-1, Interferon Gamma-Induced Protein-10 (IP-10), Monocyte Chemotactic Protein-1 (MCP-1), Macrophage-Derived Chemokine (MDC), Macrophage Inflammatory Protein-1 beta (MIP-1β), Thymus and Activation Regulated Chemokine (TARC), and Brain Derived Neurotropic Factor (BDNF). Post-hoc analyses revealed an overall pattern of higher levels of IL-10, MCP-1, MIP-1β, TARC, and BDNF in CHR as compared to FEP-a, FEP-n, and HC subjects.

Corresponding Author: Kristin Cadenhead, M.D., Professor Department of Psychiatry, University of California, San Diego, CA, 9500 Gilman Drive, 0810, La Jolla, CA 92093-08109500, Phone: 619-543-6445, Fax: 619-543-7315, kcadenhead@ucsd.edu.

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Conclusions.—Results reveal a profile of immuno-inflammatory dysregulation in early stages of psychosis prior to psychotic conversion and treatment with antipsychotic medication. The CHR phase of early psychosis may represent a period of increased immuno-inflammatory activation, but due to limited sample size, these results deserve replication in a well characterized early psychosis population.

1. INTRODUCTION

Research examining the role of immuno-inflammatory processes in the development of psychosis spectrum disorders has produced inconsistent results (Baumeister et al., 2016; Tourjman et al., 2013). Immune system regulation is associated with a variety of variables including age, weight, tobacco use, and psychotropic medication. These variables are inconsistently controlled for across studies of inflammation, perhaps contributing to mixed results. The influence of antipsychotic medication on inflammation in psychosis is not only relevant for reliable findings in immuno-inflammatory research, but also for understanding mechanistic pathways of disease progression in psychosis, thus informing development and implementation of more effective intervention techniques.

1.1 Inflammatory Analytes in Early Psychosis

Neurodevelopmental models of psychosis emphasize the role of immuno-inflammatory changes, oxidative stress, and hormonal changes in disease onset and progression. The hypothalamic-pituitary-adrenal (HPA) axis is responsible for the release of glucocorticoids in the brain that signal activation of coordinated autonomic, neuroendocrine, metabolic, and immune system responses (Lupien et al., 2009). Importantly, the HPA axis is highly responsive to environmental adversities both in childhood and in adulthood (Tsigos and Chrousos, 2002). Findings are inconsistent as to whether childhood trauma or early life stress leads to exclusively hyper-activation versus hypo-activation of HPA-axis glucocorticoid release (Heim et al., 2001; Heim et al., 2000; Heim et al., 2008; Heim et al., 2002; Heim et al., 2010), but nonetheless, *dysregulation* of HPA- axis has been associated with the development of both mental and physical illnesses, including increased risk for cardiac disease, diabetes, obesity, and autoimmune disorders (Lupien et al., 2009). In fact, the overlap between physical and mental illness resulting from exposure to childhood trauma and HPA-axis dysregulation, has led to the exploration of the role of immune system as an underlying mechanism in psychopathology, as inflammation is involved in the pathogenesis of many of the aforementioned medical disorders associated with childhood trauma and HPA-axis dysregulation (Nemeroff, 2004).

Additionally, it has been suggested that infection or physiological insults during the perinatal period may prime the immune system, making the individual more vulnerable for later-life alterations in cytokine production, as well as changes in cognitive function and mood dysregulation in the future (Bland et al., 2010). Perinatal inflammation may stand at the top of a cascade of complex neural and systemic events that disrupt cell structure and function, leading to later-life sensitivity to immune challenges in psychosis as seen in neurodegenerative diseases (Bilbo and Schwarz, 2009; Meyer et al., 2005). In later life, the release of pro-inflammatory cytokines by prolonged microglial hyperactivity and peripheral

immune activation may lead to neuronal apoptosis, which is seen in neurodegenerative disorders such as Parkinson's Disease and Alzheimer's Disease, and may be related to the loss of grey matter observed in patients with schizophrenia (Block and Hong, 2005; McGeer et al., 2016; Monji et al., 2013). Thus, experience of early life trauma, including infection, injury, or psychosocial trauma is associated with significantly increased lifetime risk for developing serious mental illnesses, such as major depressive disorder (MDD; Danese and Baldwin, 2017; Mandelli et al., 2015), bipolar disorder (BD; Agnew-Blais and Danese, 2016), post-traumatic stress disorder (Perry, 1994), schizophrenia (SCZ) (Varese et al., 2012), as well as personality disorders (Carr et al., 2013) and substance use disorders (Huang et al., 2011).

Expanding genomic research has led to discoveries as to how exposure to early-life complications (such as maternal infection) influence cumulative risk for schizophrenia via effects on placental gene expression (Ursini et al., 2018). For example, Ursini et al. (2018), report that genes identified through schizophrenia genome-wide association studies (GWAS) have been shown to be differentially expressed in the placenta in response to early life biological stressors in those individuals who go on to develop schizophrenia in adulthood. Thus, measuring the impact of environmental stress on risk for developing schizophrenia through blood plasma analytes (genes, cytokines, chemokines, etc.) has become a new frontier for research on the etiology of psychotic disorders and potential target for intervention. Determining a reliable profile of immuno-inflammatory changes across early phases of psychotic illness is a necessary step in determining how blood measurements of immune system dysregulation may serve as a potential biomarker for disease progression and target for therapeutic intervention.

1.1.1 Immuno-Inflammatory Changes in Clinical High-Risk Youth.—

A limited number of studies have explored differences in levels of immuno-inflammatory analytes between CHR and HC groups, as the primary study aim (not including multiplex inflammatory biomarker studies that analyze prediction of psychotic conversion). Stojanovic et al. (2014) reported that levels of plasma IL-6 were significantly higher in CHR subjects as compared to HC subjects. Zeni-Graiff et al. (2016) later replicated the IL-6 results, additionally reporting that levels of IL-17 were significantly lower in CHR subjects as compared to HC subjects. Karanikas et al. (2017) report significantly higher levels of IL-4 in CHR as compared to HC subjects. Focking et al. (2016) report that individuals identified to be at "ultra-high risk" for developing a psychotic disorder, demonstrate elevations in baseline levels of plasma IL12/23p40 compared to healthy controls and that elevations of this marker were associated with transition to a psychotic disorder. Yee et al. (2018) report significantly higher levels of serum BDNF in CHR subjects as compared to healthy controls, although the elevation was not predictive of transition to psychosis. Finally, Goldsmith et al. (2019) demonstrated that baseline TNF-α and IL-6 levels predicted negative symptom trajectories in CHR individuals.

Thus, there appears to be evidence of increased levels of several inflammatory analytes in individuals at heightened risk for psychosis, but how these elevations compare to elevations of inflammatory analytes across later phases of psychotic illness remains unclear. Further, CHR groups tend to be rather heterogenous, with 20–35% of CHR individuals developing

full psychotic symptoms over a 2-year period (Cannon et al., 2016; Fusar-Poli, 2012), so it is unclear whether these early findings are specific to psychosis risk or general psychopathology and environmental factors.

1.1.2 1 Immuno-Inflammatory Changes in First Episode Psychosis.: Although research on levels of inflammatory analytes in FEP subjects has been more prolific, it is also more inconsistent. A recent systematic review (Schiavone and Trabace, 2017) aggregated 59 studies of cytokine levels in early psychosis subjects, reporting evidence for significantly higher levels of circulating cytokines, IL-6, IL-1β, IL-2, IL-4, IL-10, TNF-α, and IL-8, in FEP as compared to HC groups. However, these results are not consistent across studies, with evidence from several studies demonstrating significantly higher levels of analytes only in drug naive FEP subjects and no significant differences in levels of analytes (IL-6, IL-2, IL-4, IL-10, TNF-α, and IL-17) between FEP compared to HC subjects (Schiavone and Trabace, 2017). The effect of antipsychotic medication on inflammatory analytes is an important variable that has been inconsistently examined in current inflammatory research.

Additionally, there have been few studies investigating levels of chemokines between FEP and HC subjects, with only one study examining MCP-1 in FEP subjects (Martínez-Cengotitabengoa et al., 2012). Martínez-Cengotitabengoa et al. (2012) examined the association between MCP-1 and cognition in FEP subjects, reporting that MCP-1 was strongly associated with learning and memory, consistent with findings that MCP-1 is associated with cognitive deficits in Alzheimer disease (Galimberti et al., 2006) and HIV dementia (Monteiro de Almeida et al., 2005). More research is needed to explore the role of chemokines in early psychosis, particularly if these analytes are associated with cognitive decline and other relevant impairments in psychotic illness.

More consistently, levels of BDNF have been reported to be significantly reduced in drug naïve FEP subjects, as compared to HC subjects (Toll and Mane, 2015). Importantly, Toll and Mane (2015) discuss that only studies conducted with drug-naïve FEP subjects demonstrated reductions in BDNF levels compared to HC subjects. In contrast, studies in antipsychotic medicated FEP subjects report no alterations levels of BDNF compared to HC subjects. These results are consistent with previous meta-analyses in drug-naïve schizophrenia groups (Green et al., 2011), as well as subsequent studies, which additionally report that levels of BDNF are generally reduced in drug-naïve FEP patients and appear to be associated with learning capacity and cognition (Ruiz de Azua et al., 2013); however, reductions in BDNF have not been reported to be associated with psychotic symptom severity nor predictive of conversion to psychosis (Simsek et al., 2015).

Despite inconsistent findings looking at differences in individuals analytes, several studies (Chan et al., 2015; Perkins et al., 2015; Schwarz et al., 2012; Schwarz et al., 2014) have demonstrated the clinical relevance of immuno-inflammatory changes in psychosis groups through development of blood-based protein biomarker multiplexed immunoassays that either discriminate individuals with a psychotic disorder from HC subjects or reliably predict which CHR individuals will go on to develop a psychotic disorder. In unmedicated FEP subjects, Schwarz et al. (2012) identified inflammatory, oxidative stress, and HPA signaling serum proteins that were uniquely altered in FEP subjects. As part of the North American

Prodrome Longitudinal Study (NAPLS) project, Perkins et al. (2015) identified a multiplex blood assay that reliably distinguished participants at clinical high risk (CHR) for psychosis from unaffected comparison subjects and predicted which CHR subjects are likely to transition to an acute psychotic disorder. Chan et al. (2015) established a biomarker panel with high discriminatory power to differentiate CHR individuals who would later be diagnosed with schizophrenia versus a diagnosis of bipolar disorder. Overall these studies demonstrate that early psychosis may be a period of immuno-inflammatory change that is clinically relevant to disease progression. There is significant importance in identifying markers for disease risk in CHR as well as personalizing treatment for those patients that appear to have more immuno-inflammatory dysregulation.

Inflammatory changes have also been associated with symptom psychosis severity and treatment outcome. Mondelli et al. (2015) demonstrate that at first onset of psychosis, those individuals who did not respond to treatment demonstrated higher levels of IFN-γ and IL-6 as compared to treatment responders. Associations between inflammatory analytes, psychotic symptoms severity, and functioning has been well studied in patients with chronic psychosis (Hong et al., 2017; Lee et al., 2017), but less extensively in FEP and CHR subjects. In schizophrenia groups, higher levels of pro-inflammatory cytokines TNF-α and IL-6 have been associated with higher levels of depressive symptoms, greater physical comorbidities, such as arthritis, reduced executive functioning, and lower self-rated mental well-being, suggesting that these markers are clinically relevant (Lee et al., 2017). Similarly, levels of chemokines MCP-1, MIP-1β, Eotaxin-1, and MDC have been observed to not only be higher in patients with schizophrenia compared to healthy controls, but also significantly associated with increased levels of subclinical depressive symptoms, worse self-rated mental well-being, and greater overall severity of typically mild medical illnesses (Hong et al., 2017).

1.2 The Effect of Antipsychotic Medication on Inflammatory Analytes in Psychosis

Antipsychotic medication has been shown to influence the production of peripheral inflammatory markers in both human (Baumeister et al., 2016; Tourjman et al., 2013) and animal models (MacDowell et al., 2013; Sugino et al., 2009). In a meta-analysis, Tourjman et al. (2013), report that antipsychotic treatment is associated with moderate decreases in levels of cytokines IL-1β and IFN-γ in patients with schizophrenia, as well as increases in sIL-2R and IL-12. Baumeister et al. (2016) report that typical antipsychotic medications (haloperidol and chlorpromazine) have been associated with inconsistent effects on IFN-γ, IL-4 IL-2, IL-10, and TNF-α, with no significant augmentation of IL-6 reported across studies. Further, Baumeister et al. (2016) report mixed findings with atypical antipsychotic medications on IL-6, IFN-γ, TNF-α, with the most consistent effects for quetiapine and risperidone attenuating TNF-α and clozapine attenuating IL-6.

Since the meta-analysis of Tourjman et al. (2013) and systematic review of Baumeister et al. (2016) several studies have examined the relationship between inflammatory analyte levels and initiation of antipsychotic medication in drug naïve FEP subjects. Borovcanin et al. (2013) observed lower levels of IL-4, IL-6, and IL-27 in antipsychotic naïve FEP patients following treatment with antipsychotic medication. Song et al. (2014) report that risperidone

treatment in drug naïve FEP subjects was associated with an initial decrease in IL-1β and IL-6 levels during the first few weeks of treatment, followed by a gradual increase of these cytokines after 3–6 months of treatment, as well as progressive weight gain and increases in TNF-α levels. Similarly, Haring et al. (2015) report that levels of epidermal growth factor (EGF), IL-2, vascular endothelial growth factor (VEGF), IL-6, IFN-γ, IL-4, IL-8 and IL-1α were significantly lower in previously antipsychotic naïve FEP subjects, 7 months post-antipsychotic treatment as compared to pre-medication levels; however, while psychotic symptom severity significantly decreased following antipsychotic treatment, Haring et al. (2015) report that body mass index (BMI) significantly increased. Noto et al. (2014) also report reductions of IL-4, IL-6, IL-10, and TNF-α levels in drug naïve FEP subjects following treatment with antipsychotic medication. Finally, Juncal-Ruiz et al. (2018) report decreased levels of IL-8, MIP-1β, Fractalkine, TNF-α, IL-7, IL-13, IL-17α, IL-23, and IL-21 three months post treatment with risperidone and aripiprazole.

Exposure to or active use of antipsychotic medication is not always considered as a confounding variable in inflammatory biomarker analyses in individuals with schizophrenia, perhaps contributing to the inconsistent results. If antipsychotic medication exposure is controlled for in studies, the method by which it is controlled remains inconsistent, with some studies controlling for duration of exposure and others recruiting drug naïve FEP groups.

Peripheral cytokine and chemokine levels are affected by a variety of other clinical and systemic factors, such as, obesity (Leonard et al., 2012), glucose intolerance (DeMarco et al., 2010), and metabolic syndrome (Barzilay et al., 2001). The development of metabolic abnormalities is a side effect of prolonged antipsychotic exposure (Jeon and Kim, 2017; Yogaratnam et al., 2013). Making matters even more complex, metabolic abnormalities including obesity, hypertension, and elevated blood pressure have been reported to occur in antipsychotic-naïve early psychosis groups (Cadenhead et al., 2018; Correll et al., 2014), suggesting that metabolic disturbances could be reflective of underlying processes specific to the development of psychosis (perhaps immune activation) and not exclusively the result of exposure to antipsychotic medication.

Taken together, these results suggest that antipsychotic medication impacts levels of inflammatory analytes in two opposing ways. In initially drug naïve FEP groups, antipsychotic medication initiation is associated with a decrease in some inflammatory analytes (Baumeister et al., 2016; Haring et al., 2015; Song et al., 2014), while prolonged use of antipsychotic medication is associated with the development of metabolic abnormalities that may increase levels of inflammatory analytes (Balõtšev et al., 2017; Haring et al., 2015). These paradoxical effects become problematic for the reliable and valid measurement of inflammatory analytes across heterogenous groups of unmedicated and medicated individuals.

Overall, current inflammatory analyte findings are inconsistent, suggesting that the identification of clinically relevant and reliably predictive blood-based inflammatory analytes in psychosis is ongoing. Aside from possible inconsistencies in assay methods, the design and overall aim of existing studies vastly differ. Few studies have examined patterns

of analyte activity across stages of emerging psychosis and there has been inadequate consideration of the degree to which inflammatory analytes are stimulated or suppressed as a result of antipsychotic treatment. Existing inflammatory research in groups with chronic schizophrenia (not reviewed here) has driven the exploration of immuno-inflammatory changes in earlier phases of psychotic illness; however, patients in later-stages of psychotic illness are more likely to have been exposed to antipsychotic medication and more likely to have developed chronic medical problems that are associated with serious mental illness. Thus, significant and reliable inflammatory analyte findings across studies may be lost in the noise of temporal variation of analytes across the phases of psychotic illness, as well as muddled by the short-term and long-term effects of antipsychotic treatment and metabolic disturbances.

Preliminary inflammatory analyte data will be presented in antipsychotic-naïve subjects at clinical high risk (CHR) for developing a psychotic disorder, antipsychotic treated (-a) and antipsychotic-naïve (-n) subjects in their first episode of psychosis (FEP), and healthy control (HC) subjects, using an investigatory panel of inflammatory analytes, including: Interferon-gamma (IFN-γ), Interleukin-1beta (IL-1β), Interleukin-6 (IL-6), Interleukin-10 (IL-10), Interleukin-12p70 (IL-12p70), Tumor Necrosis Factor-alpha (TNF-α), Eotaxin-1, Eotaxin-3, Fractalkine, Interleukin-8 (IL-8), Interferon Gamma-Induced Protein-10 (IP-10), Monocyte Chemotactic Protein-1 (MCP-1), Macrophage-Derived Chemokine (MDC), Macrophage Inflammatory Protein-1 alpha (MIP-1α), Macrophage Inflammatory Protein-1beta (MIP-1β), Thymus and Activation Regulated Chemokine (TARC), and Brain Derived Neurotropic Factor (BDNF). These analytes were chosen based on a combination of factors, including review of the literature on immuno-inflammatory changes in early psychosis literature, findings in chronic psychosis (cite Hong) and unpublished findings from adolescents exposed to HIV in utero compared to controls (Burlacu et al., 2018).

1.3 Aims

The current study aimed to examine peripheral immuno-inflammatory analytes in CHR, FEP-n, FEP-a, and HC subjects to assess differences across early stages of psychosis and medicated versus unmedicated subjects. We predicted that pro-inflammatory analytes would be elevated in early psychosis subjects compared to controls and highest in those individuals who were antipsychotic naive.

2. METHODS AND MATERIALS

2.1 Participants

The current study is an analysis of peripheral analyte data collected as part of several studies. Treatment seeking individuals and healthy controls (HC) (ages 12-40) were recruited between the dates of 10/03/2013 to 05/01/2017 at two sites, University of California, San Diego (UCSD) Cognitive Assessment and Risk Evaluation (CARE) Early Psychosis Treatment Center in San Diego, California and the Emergency Department, the First-Episode Psychosis Clinic, and the Adolescent Program of Neuropsychiatric and Imaging Study, PIENSA, of the Instituto Nacional de Neurología y Neurocirugía (INNN) in Mexico City, Mexico. The results are intended to be pilot-data for future projects.

CHR participants were considered eligible if they met criteria for at least one of three psychosis-risk syndromes as measured by the Structured Interview for Psychosis Risk Syndromes (SIPS; (Miller et al., 1999). FEP participants were considered eligible if they met criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, or psychosis NOS as assessed by the DSM-IV—SCID (APA, 1994), with onset within the past year. Healthy Control (HC) participants were considered eligible if they did not meet DSM-IV criteria for any SCID diagnosis (Axis I or Axis II) and did not have first degree relatives with a psychotic disorder. Exclusions for all participants included: concomitant medical, including inflammatory systemic illness, neurological illness, history of significant head injury (loss of consciousness greater than 15 minutes, neurological sequelae), alcohol or drug abuse (excluding nicotine) in the past month or dependence in the past three months, screening full scale estimated IQ < 80, active suicidal or homicidal ideation, pregnancy or lactation, and use of antipsychotic medication in the previous month. Although not exclusionary, all CHR subjects were antipsychotic naïve. Exposure to other psychotropic medications was not exclusionary for any groups. Cannabis use was also not exclusionary, but subjects were not eligible if they met criteria for current substance dependence. The study was approved by both UCSD and INNN Institutional Review Boards. All participants provided written informed consent. Participants under the age of 18 provided assent in conjunction with parental consent.

2.2 Measures

Sociodemographic information, medical, treatment, and family history were collected through participant interview or review of records with authorization. In CHR subjects, diagnostic assessment and psychosis-risk symptoms severity were assessed through the Structured Interview for Psychosis Risk Syndromes (SIPS; (Miller et al., 1999). In FEP subjects, severity of psychotic symptoms was assessed using the Positive and Negative Symptom Scale (PANSS; (Kay et al., 1987).

2.3 Procedures

An investigatory panel of inflammatory analytes (Table 1) was chosen collaboratively, based on the early psychosis literature and in consultation with Dr. Cristian Achim in the NeuroAIDS program at UCSD. Our panel includes not only markers that have been shown to differ across psychosis-spectrum groups, but also analytes associated with neurocognitive deficits in HIV exposed adolescents (Burlacu et al., 2018).

Participants at both sites (San Diego and Mexico City) completed fasting blood draw between 8:00-11:00 a.m. using consistent procedures. Venous blood for biomarker assays was collected using EDTA vacuum tubes using standard phlebotomy procedures, and plasma was collected after centrifugation. In order to guarantee consistent analyses and reduce assay variation, the Mexico City blood specimens were shipped on dry ice to the San Diego site and all samples were assayed at the same time and location. Plasma was stored at −80 °C until assays were performed. All samples were assayed by a single laboratory technician who was blinded to participant identifiers and subject diagnosis. Analytes were measured using commercially available immunoassays and run according to the manufactures' protocol.

Plasma cytokine levels were quantified using Meso Scale Discovery (MSD) MULTI-SPOT® Assay System and analyzed on a MESO QuickPlex SQ 120 (Rockville, MD, USA). Using MSD Discovery Workbench® 4.0 analysis software, standard curves were formed by fitting ECL signal from calibrators to a 4-parameter logistic model with a 1/y2 weighting. Samples were run in duplicates, using V-PLEX Human Chemokine Panel (VPLEX catalog #K15047D) to measure the chemokines, V-PLEX Human Proinflammatory Panel (VPLEX catalog #K15049D) was used to assay pro-inflammatory marker levels, and MULTI-SPOT 4 Spot Cytokine custom Human BDNF catalog #N451A-1 was used to measure BDNF. V-PLEX kits are fully validated according to fit-for-purpose principles and the FDA's analytical validation guidelines according to the manufacturer (Meso Scale Discovery). Due to sample size, samples were run on 3 assay plates. Biomarker precision was ensured by assaying specimens in duplicate with internal controls. Inter-assay coefficient of variation (CV%) for all analytes was below 10%. Intra-assay CV% was below 10% for all analytes except for Eotaxin-3 (12.4%), MIP-1α (37.39%), IL-12p70 (27.46%) and IL-1β (25.42%). The lowest detected level for each marker was as follows: 0.131 pg/mL (IFN-γ), 0.0072 pg/mL (IL-1β), 0.0294 pg/mL (IL-6), 0.0153 pg/mL (IL-10), 0.0345 pg/mL (IL-12p70), 0.102 (TNF- α), 0.03 pg/mL (IP-10), 1.75 pg/mL (MDC), 0.02 pg/mL (MCP-1), 1.78 pg/mL (MIP-1α),0.21 pg/mL (MIP-1β), 0.04 pg/mL (TARC), MDC, Fractalkine, 1.97 pg/mL (Eotaxin-1),0.76 pg/mL (Eotaxin-3), 0.05 pg/mL (BDNF). No sample showed marker levels below the detection limits.

2.4 Statistical Analysis and Data Analytic Plan

Independent samples t-tests, one-way analysis of variance (ANOVA), and chi-squared analyses were used to assess sample characteristics of and group differences in age, race, ethnicity, sex, and medication status. An alpha level of 0.05 was used for all analyses. Mean concentrations of each biomarker were log transformed to decrease the variability of data and make data conform more closely to the normal distribution. One-way multivariate analysis of covariance (MANCOVA) was used to assess group differences among the log transformed mean concentration values for each biomarker, with age as a covariate. Post-Hoc comparisons were conducted using the Bonferroni procedure.

3. RESULTS

3.1 Sample Characteristics

As seen in Table 2, a total of 68 participants were included in this study, including: 50 FEP (FEP-med=10), 11 CHR, and 7 HC subjects. Groups did not differ in sex. Bonferroni Post-Hoc analyses revealed that FEP-n and CHR groups differed in age ($p<0.005$). Groups also differed in race and ethnicity; however, these differences were expected due to geographic location of our sites (i.e., Mexico City). For this reason, there were significantly more Latino than non-Latino subjects, as well as interracial subjects as compared to other racial groups in this sample.

FEP-a and FEP-n subjects significantly differed in psychotic symptom severity (Table 3). As expected, FEP-n subjects demonstrated significantly higher scores across PANSS positive, negative, general, and total symptom severity scores, compared to FEP-a subjects.

3.2 MANCOVA Group Comparison: Inflammatory Analytes

Consistent with our hypothesis, several inflammatory analytes significantly differed between groups (Table 4), including: IFN-γ, IL-10, Eotaxin-1, IP-10, MCP-1, MDC, MIP-1β, TARC, and BDNF. Post-Hoc comparisons, using the Bonferroni procedure, revealed that CHR subjects exhibited significantly higher mean concentration values of MCP-1, MIP-1β, TARC, and BDNF compared to FEP-n, FEP-a, and HC subjects (Figure 1).Eotaxin-1 was significantly higher in both CHR and FEP-n groups as compared to FEP-a and HC groups. MDC was significantly higher in both CHR and FEP-a subjects as compared to FEP-n subjects. CHR subjects demonstrated significantly higher levels of IFN-γ as compared to FEP-n subjects. Finally, levels of IL-10 did not significantly differ during post-hoc comparisons despite demonstrating an overall group difference during between-subjects analyses.

Taken together, these results reveal a profile of higher levels of inflammatory analytes in CHR subjects as compared to FEP and HC subjects, with the exception of Eotaxin-1 and MDC. Eotaxin-1 appears to be elevated in both the antipsychotic naive CHR and FEP-n groups as compared to FEP-a and HC groups, while MDC appears to be elevated in both the antipsychotic naive CHR and FEP-a groups as compared to FEP-n and HC groups.

FEP-a and HC subjects did not significantly differ in peripheral plasma levels across any analytes, which is meaningful as this may suggest that antipsychotic medication has an anti-inflammatory effect early in psychosis.

4. DISCUSSION

To our knowledge this is the first study to investigate immuno-inflammatory profiles across HC, CHR, antipsychotic medicated FEP-a, and antipsychotic naïve FEP-n groups. Consistent with previous research, individuals in the FEP and CHR groups demonstrated higher levels of pro-inflammatory cytokines and chemokines as compared to HC subjects. These results provide preliminary evidence that 1) immune activity is dysregulated early in the development of psychosis in antipsychotic naïve CHR and FEP patients and 2) antipsychotic medications may have an anti-inflammatory effect early in the disease process. More specifically, CHR individuals showed significantly higher levels of multiple immune markers (MCP-1, MIP-1β, TARC, and BDNF), as compared to both FEP-a and HC groups even when controlling for age. Further, FEP-n and CHR subjects demonstrated higher levels of Eotaxin-1 compared to both HC and FEP-a subjects while, in contrast, FEP-a and CHR subjects demonstrated higher levels of MDC compared to both HC and FEP-n subjects. Although it could be argued that the elevation of inflammatory analytes in the CHR group may be reflective of developmental changes, age was controlled across analyses. Although only 2 of the CHR sample are known to have converted to psychosis, it is possible that the prodromal period of psychosis represents a clinically significant period of immune activation or dysregulation. For example, in a longitudinal study conducted by Duffy et al. (2014), subjects at risk for developing bipolar disorder were shown not only shown to have higher levels of IL-6 and BDNF as compared to controls, but also significantly higher levels of these analytes earlier in the trajectory of illness as compared to later in the illness progression. Thus, note only relevant to psychosis, clinically significant changes in immuno-

inflammatory analytes may be detectable across stages of illness. Although not part of the current study, it would be meaningful for future studies to explore immuno-inflammatory changes in conjunction with functional decline and psychotic symptom progression to more meaningfully interpret higher levels of analytes in earlier versus later stages of illness progression. Further, exploring the associations between peripheral immuno-inflammatory changes, microglial activity, and gray matter volume will be an important step in exploring correlations between the neural and peripheral inflammation. For example, Bloomfield et al. (2016) demonstrated that microglial activity, measured using translocator-protein positron emission tomography (PET) imaging, is not only increased in unmedicated CHR subjects, but also associated with increases in peripheral proinflammatory cytokines and reductions of gray matter volume after controlling for a translocator-specific genetic polymorphism.

Overall, antipsychotic naïve CHR subjects demonstrated higher levels of inflammatory analytes as compared to FEP-a, FEP-n, and HC subjects. These results are similar to existing research on the effects of antipsychotic medication in drug naïve FEP subjects, where antipsychotic medication appears to initially decrease levels of inflammatory analytes within the first year of treatment (Baumeister et al., 2016; Haring et al., 2015; Juncal-Ruiz et al., 2018; Noto et al., 2014; Song et al., 2014). However, given the cross-sectional design of this study, conclusions cannot be drawn from this study as to whether prolonged use of antipsychotic medication ultimately leads to increased levels of inflammatory analytes nor can we conclude whether or not increases in analytes post antipsychotic medication initiation are a direct result of medication versus potential systemic factors associated with progression of psychotic illness. Nonetheless, these results emphasize the importance of recruiting drug naïve groups, as antipsychotic medicated individuals in this study showed no significant differences in analyte levels as compared to controls. In the current study merely controlling for duration of antipsychotic usage would have washed out meaningful differences in analyte levels between antipsychotic treated and naïve groups. Ultimately, the complex interplay of immune system activation/suppression in the development of psychosis and co-morbid systemic illnesses will only be fully understood through the recruitment of drug naïve groups in prospective research designs. Controlling for duration of antipsychotic medication exposure/use is simply not enough when the goal is to unveil a reliable profile of inflammatory analytes representative of mechanistic disease pathways in psychosis. The examination and understanding of associations between inflammatory analytes and neurocognition, social cognition, and/or functional capacity across stages of emerging psychosis will be important for future research.

Previous research, using blood based markers of immuno-inflammatory changes to develop tests for identification of psychosis before disease onset, demonstrates that that elevations in a select set of inflammatory analytes may reliably discriminate between individuals who develop psychosis and those who do not (Chan et al., 2015; Domenici et al., 2010; Perkins et al., 2015; Schwarz et al., 2012; Schwarz et al., 2014). However, studies examining the temporal variation in levels of inflammatory analytes across CHR, FEP, HC, and chronic phases of psychotic illness have been largely missing. *This study has shown that analytes previously reported as significant predictors of psychosis or discriminators between psychosis and healthy groups (*Table 6*) are elevated during the at-risk phase of illness, and may decrease after the conversion to psychotic illness has occurred (i.e. the transition from*

CHR to FEP) and possibly the initiation of antipsychotic medication. As seen in Table 6, many of the immune markers investigated in this study have been shown to reliably discriminate between individuals with psychosis spectrum disorders as compared to controls in previous research. Of the inflammatory analytes shown to significantly differ across groups in the current study, Eotaxin-1, IL-10, MCP-1, MDC, MIP-1β, and BDNF were each shown to differ between individuals with schizophrenia as compared to healthy controls in *at least* 2 previous studies. These results provide support for the inclusion of more extensive inflammatory marker panels in future research. In the current study, 6 of our 8 significant findings were chemokines, which have not been as extensively investigated in early psychosis as cytokines.

If immune system activation is integral to the complex cascade of events that may lead to the development of devastating neurodevelopmental diseases such as schizophrenia, then treatment interventions that target immuno-inflammatory abnormalities or perhaps the neurotoxic processes that stimulate inflammatory responses, could be prophylactic. However, uncovering the role of the immune system function in psychopathological dysfunction will be an iterative process. Psychoneuroimmunology has emerged as a new frontier in research on the etiology of psychopathological dysfunction with researchers seeking to understand the complex relationship between the immune system and mental health. However, in order to accomplish this goal, recruitment of antipsychotic naïve early psychosis groups is fundamental, as medication exposure could lead to inconsistent findings.

4.1 Limitations.

Several important limitations to this study should be considered when interpreting results. This study was an analysis of existing pilot data and therefore analyses could not be fully powered. The limited sample size may affect the replicability of results, nonetheless, these findings present novel information regarding the differences in inflammatory profiles across different stages of psychotic illness and can inform future research studies. The design is cross-sectional, preventing the ability to draw causal conclusions regarding the role of immuno-inflammatory changes in the disease pathology of emerging psychosis, as well as full assessment of differences between anti-psychotic naïve and antipsychotic treated groups. Although significant results persisted after adjusting for sociodemographic characteristics including age and gender, the potential effects of these variables should not be underestimated. In addition, the effects of tobacco use and BMI were not investigated in this current study, as those variables were not available for all subjects. Experience of childhood trauma, which is known to have an association with inflammatory variables, was also not assessed in this sample and thus investigation of the impact of childhood trauma on inflammation unfortunately could not be explored. Finally, duration of storage of samples was not collected and thus not added as a covariate in analyses. Due to unequal group sizes, variances differed across groups. Replicating results with a fully powered, prospective, case controlled, design would allow for more reliable conclusions to be drawn.

5. CONCLUSIONS

This study provides evidence that inflammatory markers are differentially expressed in pre-psychotic groups, antipsychotic naïve first episode, and antipsychotic treated first episode psychosis groups. The possible anti-inflammatory effect of antipsychotic medications may be in part responsible for inconsistent findings across studies, thus, recruitment of drug naïve early psychosis groups is critical for advancing our understanding of inflammatory markers in early psychosis. Although elevations of inflammatory analytes in CHR subjects may be associated with normative developmental changes, it is also possible that these elevations reflect immune system activation that is either a pathological and mechanistic *or* a heightened and protective response to an unidentified pathological process.

Further research will be important in determining if the results of this study can be replicated. A more highly powered, prospective *and* longitudinal research design that collects inflammatory, clinical symptom, and functional data from CHR, antipsychotic naive FEP, and HC subjects would be a reasonable next step in progressing our understanding of these findings. Longitudinal studies examining inflammatory analytes in CHR are needed to uncover meaningful differences in inflammatory analyte levels between the 20-35% of individuals who develop a psychotic disorder versus the 65-80% that do not. Future research should be aimed at 1) improving our understanding of the connection between oxidative stress, inflammatory processes, and the onset or progression of psychosis, 2) informing the field about the impact of antipsychotic medication on inflammatory analytes, 3) determining whether a reliable profile of inflammatory analytes across stages of psychosis can be established, as well as 4) guiding future efforts in the development of non-pharmacological interventions that target biological markers of disease progression in severe mental illness. The search for and validation of reliable biomarkers in psychosis is ongoing. Substantial research supports a role for inflammatory processes and stress related changes in the pathophysiology of psychosis.

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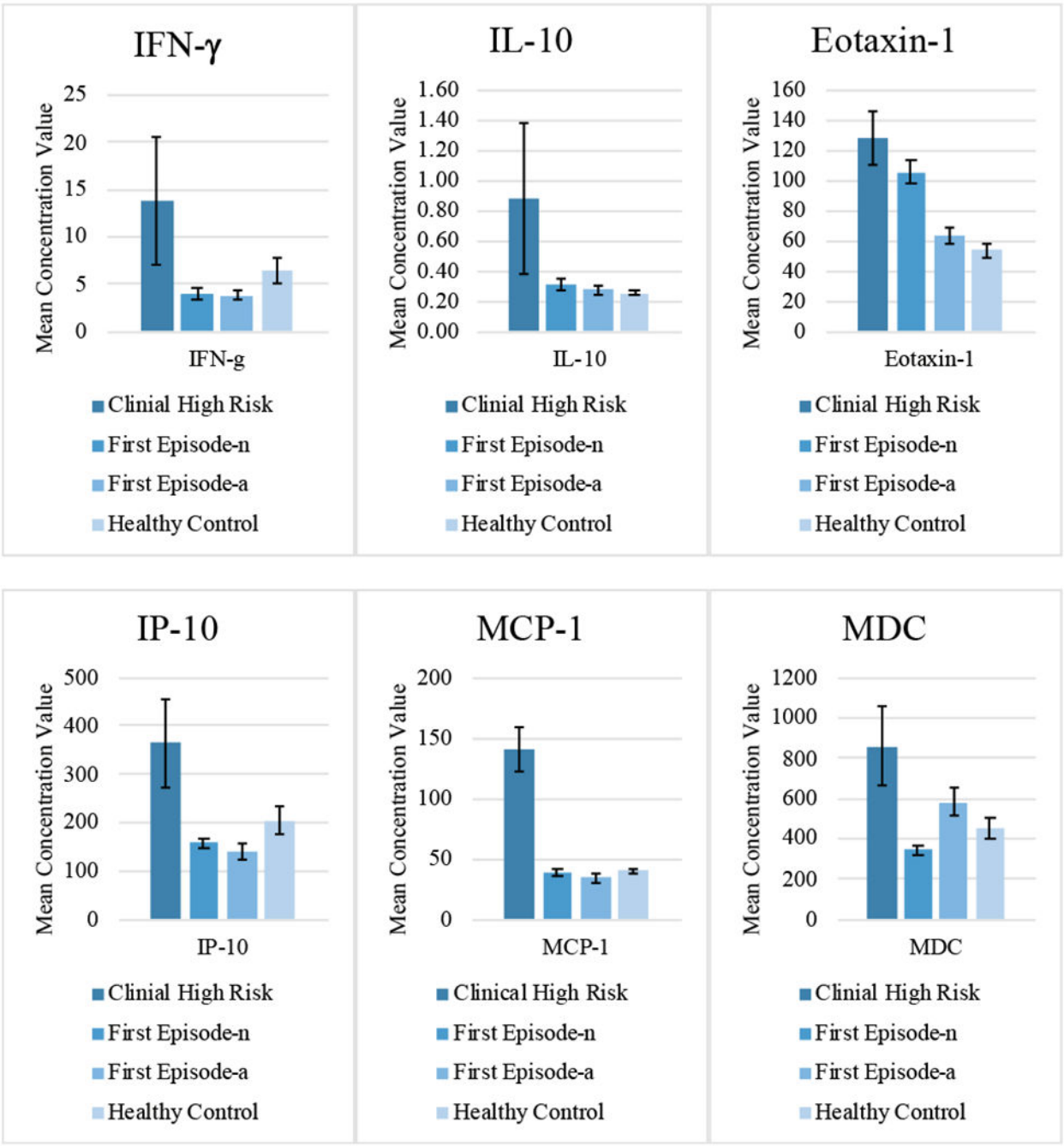

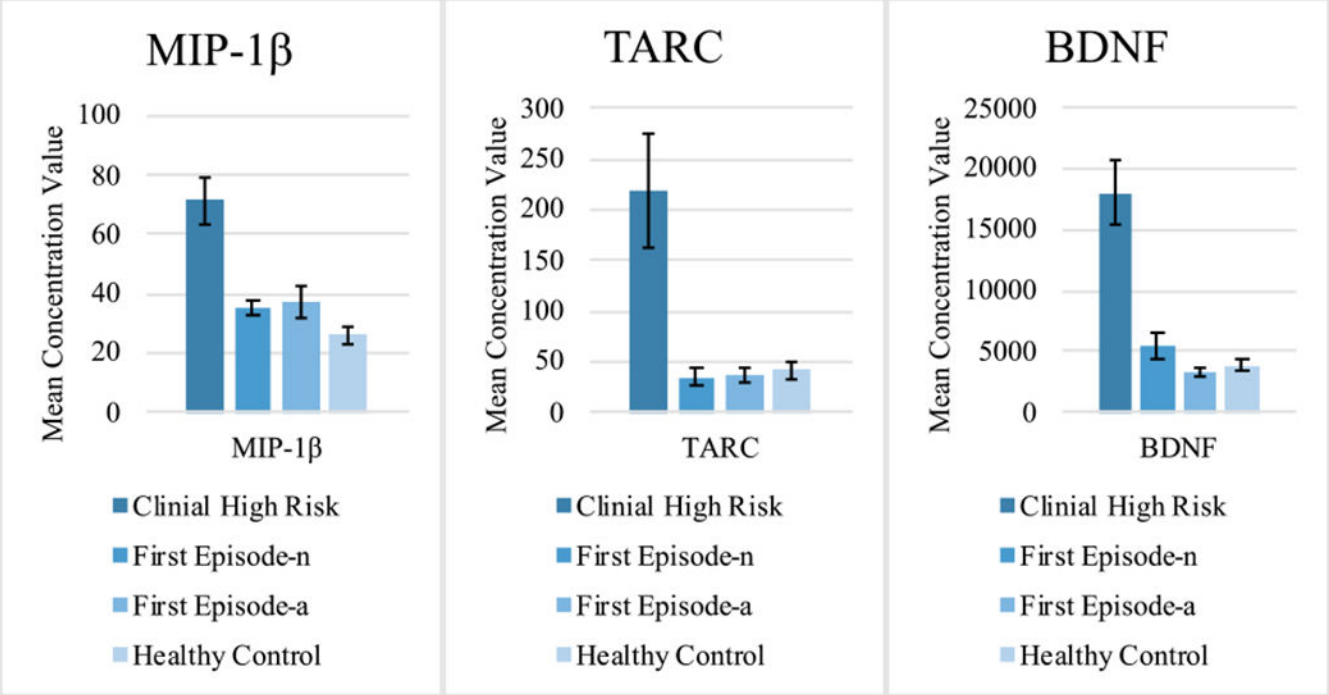

Figure 1.
Inflammatory Analytes that differed in Between Groups Comparison (N=68)

Table 1.

Inflammatory Analyte Panel: Cytokines, Chemokines, and Growth Factors

Cytokines	Chemokines	Other
Interferon-gamma (IFN-γ)	Eotaxin-1 (C-C motif chemokine ligand 11 [CCL11])	Brain Derived Neurotropic Factor (BDNF)
Interleukin-1beta (IL-1β)	Eotaxin-3 Chemokine (C-C motif) chemokine ligand 26 [CCL26])	
Interleukin-6 (IL-6)	Fractalkine (C-X3-C motif chemokine ligand 1 [CX3CL1])	
*Interleukin-10 (IL-10)	Interleukin-8 (IL-8; C-X-C motif chemokine ligand 8 [CXCL8])	
Interleukin-12p70 (IL-12p70)	Interferon Gamma-Induced Protein-10 (IP-10; C-X-C motif chemokine ligand 10 [CXCL10])	
Tumor Necrosis Factor-alpha (TNF-α)	Monocyte Chemotactic Protein-1 (MCP-1; C-C motif chemokine ligand 2 [CCL2])	
	Macrophage-Derived Chemokine (MDC; C-C motif chemokine ligand 22 [CCL22])	
	*Macrophage Inflammatory Protein-1alpha (MIP-1α; C-C motif chemokine ligand 3 [CCL3])	
	*Macrophage Inflammatory Protein- 1beta (MIP-1β; C-C motif chemokine ligand 4 [CCL4])	
	Thymus and Activation Regulated Chemokine (TARC; C-C motif chemokine ligand 17 [CCL17])	

*Suppresses Pro-Inflammatory Response

Table 2.

Sample Characteristics (N=68)

Characteristic	Total	CHR	FEP-n	FEP-a	HC	F or χ^2	*p*	*Post Hoc*
Total No.	68	11	40	10	7	3.98	0.01 *	FEP-n > CHR
Age, Mean (SD)	22.8 (6.2)	18.5 (4.7)	24.7 (6.5)	21.5 (3.4)	20.40 (4.9)			
Gender No.								
Male	50	7	29	9	5	1.98	0.58	NA
Female	18	4	11	1	2			
Race No.								
American Indian or Alaskan Native	8	2	3	3	0	46.49	$p<0.001$ ***	NA
Asian	4	1	2	0	1			
Black or African American	2	0	1	1	0			
Interracial	36	1	33	1	1			
Native Hawaiian or PI	0	0	0	0	0			
White	18	7	1	5	5			
Ethnicity No.								
Latino	46	3	35	4	4	19.24	$p<0.001$ **	NA
Non-Latino	22	8	5	6	3			
Antipsychotic Medication No.								
aripiprazole (Abilify)	2	0	0	2	0	NA		
asenapine (Saphris)	0	0	0	0	0			
cariprazine (Vraylar)	0	0	0	0	0			
clozapine (Clozaril)	0	0	0	0	0			
lurasidone (Latuda)	0	0	0	0	0			
olanzapine (Zyprexa)	2	0	0	2	0			
quetiapine (Seroquel)	0	0	0	0	0			
risperidone (Risperdal)	5	0	0	5	0			
asenapine (Saphris)	0	0	0	0	0			
Haloperidol (Haldol)	1	0	0	1	0			

* $p< 0.05$,

** $p< 0.01$,

*** $p< 0.001$

CHR= Clinical High Risk for psychosis; ***FEP-n***= First Episode Psychosis naïve to antipsychotic medication; ***FEP-a***= First Episode Psychosis antipsychotic medication treated; ***HC***= Healthy Control

Table 3.

Independent Samples T-Test: Symptom Severity and Functioning FEP-n vs. FEP-a (N= 50)

Measure	Mean (SD)		$t_{(1,57)}$	p
	FEP-n (n=40)	FEP-a (n=10)		
PANSS Positive Scale Total	**27.7 (9.0)**	14.6 (6.2)	−4.4	$p<0.001^{***}$
PANSS Negative Scale Total	**23.1 (9.9)**	13.7 (4.4)	−4.7	$p<0.001^{***}$
PANSS General Scale Total	**49.5 (14.1)**	29.9 (5.9)	−7.0	$p<0.001^{***}$
PANSS Total	**100.2 (29.9)**	58.2 (10.9)	−7.6	$p<0.001^{***}$

$^{*}p< 0.05$,

$^{**}p< 0.01$,

$^{***}p< 0.001$

FEP-n= First Episode Psychosis naïve to antipsychotic medication; ***FEP-a***= First Episode Psychosis antipsychotic medication treated; ***PANSS***= Positive and Negative Symptoms Scale

Table 4.

MANCOVA Between Groups Comparison (N=68)

Analyte		Mean pg/mL (SD)				F	*p*-value	*Partial Eta Squared*
		CHR (n=11)	FEP-n (n=40)	FEP-a (n=10)	HC (n=7)			
Cytokines	**IFN-γ** **	**13.85 (22.26)**	4.01 (3.32)	3.84 (1.79)	6.48 (3.63)	5.82	0.003 **	0.38
	IL-1β	0.06 (0.05)	0.28 (0.76)	1.67 (4.97)	0.06 (0.04)	0.84	0.49	0.08
	IL-6	0.52 (0.34)	0.65 (0.62)	0.41 (0.19)	0.52 (0.25)	0.45	0.72	0.05
	IL-10 *	**0.88 (1.81)**	0.32 (0.27)	0.28 (0.09)	0.26 (0.06)	3.53	0.03 *	0.28
	IL-12p70	0.65 (1.70)	0.25 (0.39)	0.13 (0.07)	0.18 (0.10)	0.53	0.67	0.05
	TNF-α	3.32 (0.65)	2.34 (0.83)	4.24 (4.33)	2.76 (0.24)	1.93	0.15	0.17
Chemokines	**Eotaxin-1** ***	**127.66 (58.71)**	105.88 (45.89)	64.05 (16.96)	53.99 (12.24)	7.48	$p < 0.001$ ***	0.45
	Eotaxin-3	12.81 (6.92)	14.87 (15.60)	44.16 (106.96)	32.33 (47.14)	1.10	0.37	0.11
	Fractalkine	*10770.05 (3099.28)*	9440.70 (2404.51)	10227.34 (2294.38)	10262.10 (3018.56)	2.85	0.06 ^	0.23
	IL-8	3.85 (1.44)	3.72 (9.16)	1.48 (0.70)	1.67 (0.42)	1.93	0.15	0.17
	IP-10 ***	**363.74 (296.72)**	157.79 (70.35)	140.16 (48.25)	203.17 (75.66)	8.46	$p < 0.001$ ***	0.48
	MCP-1 ***	**140.91 (59.55)**	38.07 (16.29)	34.32 (11.46)	39.98 (5.15)	25.70	$p < 0.001$ ***	0.73
	MDC ***	**860.13 (660.18)**	343.88 (140.01)	582.60 (217.01)	448.86 (142.19)	8.37	$p < 0.001$ ***	0.47
	MIP-1α	12.10 (5.70)	9.99 (4.22)	14.89 (16.85)	10.47 (7.48)	0.77	0.52	0.08
	MIP-1β ***	**71.29 (26.35)**	35.53 (14.30)	37.16 (18.86)	25.90 (7.03)	8.63	$p < 0.001$ ***	0.48
	TARC ***	**219.29 (187.88)**	35.05 (55.11)	36.51 (26.27)	41.48 (20.04)	18.52	$p < 0.001$ ***	0.67
Other	**BDNF** ***	**18082.35 (8670.79)**	5443.44(6655.26)	3306.01 (1223.24)	3875.10 (1165.39)	7.23	$p < 0.001$ ***	0.44

^ $p = 0.06$ (*trend*),

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$

CHR= Clinical High Risk for psychosis; ***FEP-n***= First Episode Psychosis naïve to antipsychotic medication; ***FEP-a***= First Episode Psychosis antipsychotic medication treated; ***HC***= Healthy Control

NOTE: Values presented in table are mean concentration value (pg/mL); however, analyses were conducted using log transformed data.

Table 5.

MANCOVA Post-Hoc with Bonferroni Corrections (N=68)

Analyte	HC vs. CHR		FEP-a vs. CHR		FEP-n vs. CHR	
	Mean Difference	***p*-value**	**Mean Difference**	***p*-value**	**Mean Difference**	***p*-value**
IFN-γ	−0.093	1.00	−0.298	0.09	−.3332 **	0.005
IL-10	−0.199	0.48	−0.179	0.49	−0.1815	0.16
Eotaxin-1	−.344 ***	p< 0.001	−.273 ***	p< 0.001	−0.0775	0.77
IP-10	−0.18	0.493	−.345 **	0.004	−.3018 ***	p< 0.001
MCP-1	−.521 ***	p< 0.001	−.60588 *	p< 0.001	−.5732 ***	p< 0.001
MDC	−0.235	0.088	−0.128	0.77	−.3579 ***	p< 0.001
MIP-1β	−.424 ***	p< 0.001	−.307 **	0.003	−.3031 ***	p< 0.001
TARC	−.665 ***	p< 0.001	−.769 ***	p< 0.001	−.8742 ***	p< 0.001
BDNF	−.601 **	0.007	−.680 ***	p< 0.001	−.6260 ***	p< 0.001
Analyte	**FEP-a vs. FEP-n**		**FEP-a vs. HC**		**FEP-n vs. HC**	
	Mean Difference	***p*-value**	**Mean Difference**	***p*-value**	**Mean Difference**	***p*-value**
IFN-γ	0.038	1.00	−0.202	0.75	−0.240	0.19
IL-10	0.002	1.00	0.020	1.00	0.017	1.00
Eotaxin-1	−.196 **	0.004	0.07	1.00	.266 ***	p< 0.001
IP-10	−0.042	1.00	−0.167	0.64	−0.129	0.87
MCP-1	−0.031	1.00	−0.083	1.00	−0.052	1.00
MDC	.230 **	0.01	0.107	1.00	−0.123	0.72
MIP-1β	−0.004	1.00	0.117	1.00	0.121	0.66
TARC	0.106	1.00	−0.104	1.00	−0.209	0.47
BDNF	−0.054	1.00	−0.079	1.00	−0.026	1.00

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$

CHR= Clinical High Risk for psychosis; ***FEP-n***= First Episode Psychosis naïve to antipsychotic medication; ***FEP-a***= First Episode Psychosis antipsychotic medication treated; ***HC***= Healthy Control

Table 6.

Analytes observed to be significantly different between SCZ or CHR vs. HC groups across a selection of blood-based biomarker studies

		FEP and chronic schizophrenia cohorts			FEP and CHR cohorts		FEP and CHR cohorts
Analyte		**(Domenici et al., 2010)**	**(Schwarz et al., 2012; Schwarz et al., 2014)**	**(Hong et al., 2017) & (Lee et al., 2017)**	**(Chan et al., 2015)**	**(Perkins et al., 2015)**	**Significant in Current Study?**
Cytokines	**IFN-γ**	NA	Yes	No	NA	NA	**Yes**
	IL-1β	No	Yes	NA	NA	Yes	No
	IL-6	Yes	No	Yes	NA	No	No
	IL-10	Yes	Yes	NA	Yes	NA	**Yes**
	IL-12p70	Yes	No	NA	NA	NA	No
	TNF-α	NA	No	Yes	NA	No	No
Chemokines	**Eotaxin-1***	Yes	Trend	Yes	Yes	No	**Yes**
	Eotaxin-3	NA	Yes	No	NA	No	No
	Fractalkine	NA	NA	No	NA	NA	No
	IL-8	Yes	No	No	Yes	Yes	No
	IP-10	NA	NA	No	NA	No	**Yes**
	MCP-1*	Yes	No	Yes	No	No	**Yes**
	MDC*	Yes	No	Yes	No	NA	**Yes**
	MIP-1α	No	No	No	NA	No	No
	MIP-1β*	Yes	No	Yes	No	No	**Yes**
	TARC	NA	NA	Yes	NA	NA	**Yes**
Other	**BDNF***	Yes	Yes	NA	NA	No	**Yes**

Yes= significantly different between groups; *No*= no differences between groups; *NA*= Not applicable, not measured in study, or not included in final analyses

CHR= Clinical High Risk for psychosis; ***FEP***= First Episode Psychosis; ***HC***= Healthy Control