Title

Does the Experience of Childhood Trauma Lead to a Pro-Inflammatory Phenotype in Youth at Clinical High Risk for Psychosis?

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Does the Experience of Childhood Trauma Lead to a Pro-Inflammatory Phenotype in Youth at Clinical High Risk for Psychosis?

A dissertation submitted in partial satisfaction of the
requirements for the degree of Doctor of Philosophy

in

Clinical Psychology

by

Skylar Kelsven

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2021

The Dissertation of Skylar Kelsven is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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2021

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VITA

EDUCATION

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PEER-REVIEWED PUBLICATIONS

1. **Kelsven, S.**, De La Fuente-Sandoval, C., Achim, C. L., Reyes-Madrigal, F., Mirzakhanian, H., Domingues, I., & Cadenhead, K. (2020). Inflammatory biomarkers in early psychosis. *Schizophrenia Research*.
2. Mahmood, Z., **Kelsven, S.**, Cadenhead, K., De La Fuente-Sandoval, C, Reyes-Madrigal, F., & Twamley, B. (2020). Compensatory cognitive training in youth at clinical high risk for psychosis. *Frontiers Psychiatry*.
3. Pinkham, A. E., Morrison, K. E., Penn, D. L., Harvey, P. D., **Kelsven, S.**, Ludwig, K., & Sasson, N. J. (2019). Comprehensive comparison of social cognitive performance in autism spectrum disorder and schizophrenia. *Psychological Medicine*, 1-9. doi:10.1017/S0033291719002708
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5. Morrison, K. E., Pinkham, A. E., **Kelsven, S.**, Ludwig, K., Penn, D. L., & Sasson, N. J. (2019). Psychometric evaluation of social cognitive measures for adults with autism. *Autism Research*, *12*(5), 766-778.
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11. Browne, J., Penn, D. L., Raykov, T., Pinkham, A. E., **Kelsven, S.**, Buck, B., & Harvey, P. D. (2016). Social cognition in schizophrenia: Factor structure of emotion processing and theory of mind. *Psychiatry Research*, *242*, 150-156.
12. Shasteen, J. R., Pinkham, A. E., **Kelsven, S.**, Ludwig, K., Payne, B. K., & Penn, D. L. (2016). Intact implicit processing of facial threat cues in schizophrenia. *Schizophrenia Research*, *170*, 150-155.
13. Pinkham, A. E., Sasson, N. J., **Kelsven, S.**, Simpson, C. E., Healey, K., & Kohler, C. (2014). An intact threat superiority effect for nonsocial but not social stimuli in schizophrenia. *Journal of Abnormal Psychology*, *123*, 168-77.
14. Simpson, C., Pinkham, A. E., **Kelsven, S.**, & Sasson, N. J. (2013). Emotion recognition abilities across stimulus modalities in schizophrenia and the role of visual attention. *Schizophrenia Research*, *151*, 102-106.

PROFESSIONAL PRESENTATIONS

1. **Kelsven, S.**, Jeffries, C., Addington, J., Bearden, C. E., Cannon, T., Cornblatt, B., Mathalon, McGlashan, T., Perkins, D., Seidman, L.J., Walker, E., Woods, S., & Cadenhead, K. (2020, June). *Does inflammation mediate the relationship between childhood trauma and psychosis?* Poster presented at the UC San Diego Judd Symposium, San Diego, CA.
2. **Kelsven, S.**, Devoe, D., Holden, J., Addington, J., Auther, A., Brummitt, K., Cadenhead, K., Cornblatt, B., Sanstesteban-Echarri, O., & Granholm, E. (2019, November). *Cognitive-behavioral social skills training in youth at clinical high risk for psychosis: Manual modifications and implementation methods*. Poster to be presented at the Association for Behavioral and Cognitive Therapies (ABCT), Atlanta, GA.
3. **Kelsven, S.**, Devoe, D., Holden, J., Addington, J., Auther, A., Brummitt, K., Cadenhead, K., Cornblatt, B., Sanstesteban-Echarri, O., & Granholm, E. (2019, April). *Cognitive-behavioral social skills training in youth at clinical high risk for psychosis: Quantitative and qualitative methods for implementation and facilitator training*. Poster presented at the Congress of the Schizophrenia International Research Society (SIRS), Orlando, FL.

4. **Kelsven, S.**, Jeffries, C., Addington, J., Bearden, C. E., Cannon, T., Cornblatt, B., Mathalon, McGlashan, T., Perkins, D., Seidman, L.J., Walker, E., Woods, S., & Cadenhead, K. (2019, April). *The association between childhood trauma and inflammation in youth at clinical high risk for psychosis*. Poster presented at the Congress of the Schizophrenia International Research Society (SIRS), Orlando, FL.

5. Brummitt, K., Author, A., **Kelsven, S.**, Devoe, D., Stern, L., Granholm, E., Cornblatt, B., Cadenhead, K., & Addington, J. (2018, October). *Cognitive behavioral social skills training for youth at risk of developing psychosis*. Poster presented at the International Conference on Early Intervention in Mental Health (IEPA), Boston, MA.

6. **Kelsven, S.**, De La Fuente-Sandoval, C., Achim, C. L., Reyes-Madrigal, F., Mirzakhanian, H., Domingues, I., & Cadenhead, K. (2018, April). *Inflammatory biomarkers in early psychosis*. Poster presented at the UC San Diego Judd Symposium, San Diego, CA.

7. **Kelsven, S.**, De La Fuente-Sandoval, C., Achim, C. L., Reyes-Madrigal, F., Mirzakhanian, H., Domingues, I., & Cadenhead, K. (2017, December). *Inflammatory biomarkers in early psychosis*. Poster presented at the American College of Neuropsychopharmacology (ACNP), Palm Springs, CA.

8. **Kelsven, S.**, Addington, J., Bearden, C. E., Cannon, T., Cornblatt, B., Mathalon, McGlashan, T., Perkins, D., Seidman, L.J., Walker, E., Woods, S., & Cadenhead, K. (2017, March). *Metabolic abnormalities and omega-3 fatty acids in latinos at clinical high risk*. Poster presented at the UC San Diego Judd Symposium, San Diego, CA.

9. **Kelsven, S.**, Addington, J., Bearden, C. E., Cannon, T., Cornblatt, B., Mathalon, McGlashan, T., Perkins, D., Seidman, L.J., Walker, E., Woods, S., & Cadenhead, K. (2017, March). *Metabolic abnormalities and omega-3 fatty acids in latinos at clinical high risk*. In P. D. Harvey (Chair), *Oral Session: Clinical Trials*. Oral presentation conducted at the International Congress on Schizophrenia Research (ICOSR), San Diego, CA.

10. Perez, V., **Kelsven, S.**, Hansen, S., Sanchez, S., & Cadenhead, K. (2017, March). *Mindfulness interventions in early psychosis: A feasibility study to assess neurocognitive and biomarker outcomes*. Poster presented at the International Congress on Schizophrenia Research (ICOSR), San Diego, CA.

11. Deyoe, J., **Kelsven, S.**, Robles-Guerrero, C., Mirzakhanian, H., Perez, G., Reyes-Madrigal, F., Twamley, E., de la Fuente-Sandoval, C., Cadenhead, K., & Sanchez, S. (2017, March). *Compensatory cognitive training in high risk latino youth*. Poster presented at the International Congress on Schizophrenia Research (ICOSR), San Diego, CA.

12. Klein, H., **Kelsven, S.**, & Pinkham, A. (2017, March). *Increased social cognitive bias in subclinical paranoia*. Poster presented at the International Congress on Schizophrenia Research (ICOSR), San Diego, CA.

13. Sanchez, S., Corbett, D., Davis, T., **Kelsven, S.**, Mirzakhanian, H., Perez, G., Perez, V., Stern, L., & Cadenhead, K. (2017, March). *Conversion probability of prodromal research participants*. Poster presented at the International Congress on Schizophrenia Research (ICOSR), San Diego, CA.

14. **Kelsven, S.**, Nelson-Graham, I., Harvey, P. D., Penn, D. L., & Pinkham, A. E. (2016, October). *The effect of race, gender, and age on social cognitive performance in*

individuals with schizophrenia. Poster presented at the Society for Research in Psychopathology (SRP), New Orleans, LA.

15. **Kelsven, S.** (2016, October). *Introductions to various pathological presentations in psychiatry: Psychosis*. Guest Lecture conducted at CampNeuro: UCSD School of Medicine, San Diego, CA.
16. **Kelsven, S.**, Hansen, S., & Cadenhead, K. (2016, October). *Mindfulness in first episode psychosis: A feasibility study*. In S. Hickman (chair), *Current Research in Mindfulness*. Oral presentation conducted at the Retreat to Promote Mindfulness and Compassion Research, San Diego, CA.
17. Ludwig, K. A., **Kelsven, S.**, Pinkham, A. E., Harvey, P. D., & Penn, D. L. (2014, November). *Social Cognition and first episode psychosis: A psychometric evaluation study*. Poster presented at the Association for Behavioral and Cognitive Therapies (ABCT), Philadelphia, PA.
18. Sasson, N., Pinkham, A. E., Faso, D., Simpson, C., & **Kelsven, S.** (2014, May). *Comparing social cognitive profiles in autism and schizophrenia*. Poster presented at the International Society for Autism Research, Atlanta, GA.
19. Simpson, C., **Kelsven, S.**, Trueba, A., & Pinkham, A. E. (2013, September). *Multisensory integration during emotion perception in schizophrenia*. Poster presented at the Society for Research in Psychopathology (SRP), Oakland, CA.
20. Nichols, H. S., Pinkham, A. E., **Kelsven S.**, & Bales L. (2013, September). *Validation of an implicit measure of paranoia: The affective misattribution procedure, threat perception version (AMP-TP)*. Poster presented at the Society for Research in Psychopathology (SRP), Oakland, CA.

ABSTRACT OF THE DISSERTATION

Does the Experience of Childhood Trauma Lead to a Pro-Inflammatory Phenotype in Youth at Clinical High Risk for Psychosis?

by

Skylar Kelsven

Doctoral of Philosophy in Clinical Psychology

University of California San Diego, 2021
San Diego State University, 2021

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Rationale: Childhood adversity is strongly associated with increased risk for psychosis. Despite clear evidence for an association between childhood trauma (CT) and psychosis, the biological mechanisms that mediate the relationship between CT and clinical outcomes in psychosis remain largely unknown. The aim of this study is to better understand associations between inflammation, CT, and clinical outcomes in subjects identified to be at clinical high risk for developing psychosis (CHR) and evaluate whether inflammation mediates the relationship between CT and clinical outcomes.

Design and Methods: Participants included 67 CHR subjects and 34 unaffected comparison subjects (UC; $N = 101$) ages 12-35 who participated in the North American Prodrome

Longitudinal Study 2 (NAPLS2). Experience of CT was assessed using the Childhood Trauma and Abuse Scale. Severity of psychosis-risk symptoms was measured using the Structured Interview for Prodromal Syndromes (SIPS). Functioning was assessed using Global Assessment of Functioning (GAF) scale. Blood samples were analyzed using validated multiplex immunoassay. Group differences between UC and CHR in CT, functioning, psychosis risk symptom severity, and inflammation were evaluated using independent samples t-tests and Chi-squared tests. Two mediation models were tested to explore whether inflammation mediated the association between 1. total CT and GAF and 2. total CT and psychosis risk positive symptom severity.

Results: Compared to UC, CHR subjects demonstrated significantly higher incidence of total CT, greater severity of psychosis risk symptoms, and significantly lower global, role, and social functioning. Regression analyses revealed that total CT and a 15-Analyte Inflammatory Index uniquely predicted psychosis risk positive symptom severity ($\beta = 0.24$, $t(65) = 1.9$, $p = 0.05$) and GAF scores ($\beta = -0.26$, $t(65) = -2.25$, $p = 0.03$). Combined, these variables explained a significant proportion of variance in psychosis risk positive symptom severity ($R^2 = 0.122$) and GAF ($R^2 = 0.151$) scores.

Conclusions and Clinical Implications: The relationship between CT, increased psychosis-risk symptom severity, and decreased functioning was replicated in this study and results demonstrated novel associations between total CT, psychosis risk positive symptom severity, and GAF. This is the first study to demonstrate that CT and inflammation may have unique and additive effects on increased psychosis risk positive symptom severity and reduced global functioning in individuals at CHR for psychosis.

I. INTRODUCTION

Psychoneuroimmunology refers to the study of interactions between behavior, neural and endocrine systems, and the immune system (Ader & Cohen, 1993). Alder and Cohen (1993) state that the field of psychoneuroimmunology is intended to "emphasize the functional significance" of the relationship between mind and body systems "in addition to" and "not in place of analysis of the mechanisms governing functions within a single system." This growing field seeks to understand the associations between environmental exposures and neural, endocrine, and immune systems, as well as the consequences of inflammatory responses on human behavior, to allow for new insights into mechanistic pathways that are involved in the development of psychopathology. Thus, identifying the impact of early life adverse experiences, such as childhood trauma, on immune system regulation, and subsequent clinical outcomes, such as functioning, provides important information regarding possible therapeutic targets for early intervention and prevention of psychopathology. Psychiatric illnesses that begin during adolescence and disrupt successful transition into adulthood represent one such category of mental disorders for which primary prevention is key, but therapeutic targets meeting the goal of prevention are lacking. This study seeks to provide rationale for and test the hypothesis that immune system dysregulation may serve as a biological mediator between the experience of childhood trauma and vulnerability for developing psychosis by evaluating associations between childhood trauma, inflammation, and clinical outcomes in a sample of subjects at clinical high risk for psychosis (CHR).

1.1 Childhood Trauma and Risk for Psychopathology

Childhood trauma is defined as the experience of severe and/or chronic interpersonal stress including abuse (sexual, physical, or emotional) or neglect (physical or emotional)

(Bernstein, Ahluvalia, Pogge, & Handelsman, 1997). In the development of a validated childhood trauma assessment tool, the Childhood Trauma Questionnaire (CTQ), Bernstein et al. (1997) defined subcategories of childhood trauma as follows: 1) sexual abuse is defined as sexual activity between a minor child (younger than17 years of age) and an adult or older person (at least 5 years older than the child); 2) Physical abuse is defined as bodily assault imposed upon a minor by an adult, which resulted in risk or experience of injury; 3) Emotional abuse is defined as verbal assaults on an individual's sense of worth or well-being, including verbal humiliation, intimidation, or demeaning behavior directed towards a minor by an adult; 4) Physical neglect is defined as the failure of caretakers to provide for a child's basic physical needs, including food, clothing, shelter, safety, and health care, as well as poor parental supervision if such behavior places a minor's safety in jeopardy; and 5) Emotional neglect is defined as a failure for a caretaker to provide a minor with appropriate emotional support or validation.

Subtypes of trauma differ in prevalence. The United States Department of Health and Human Services Administration for Children and Families report that the national number of children receiving a child protective services investigation response increased 10.0% percent from 2013 (3,184,000) to 2017 (3,501,000), with the national rounded number of victims in 2017 approximated at 674,000 children. Three-quarters (74.9%) of these victims experienced neglect, 18.3 percent physical abuse, and 8.6 percent sexual abuse (U.S. Department of Health & Human Services, 2019). However, prevention of childhood trauma extends far beyond mere desire to protect children, as research has established that the consequences of childhood trauma are severe and long-lasting. Firstly, experience of childhood trauma increases risk for medical illnesses such as lung disease, arthritic disorders, cardiac disease, diabetes, and autoimmune

disorders (Goodwin & Stein, 2004). Moreover, the development of medical disorders is found to be directly proportional to the number and magnitude of childhood traumas experienced (Dube et al., 2009; Felitti et al., 1998; Nemeroff, 2016). Secondly, experience of childhood trauma is associated with significantly increased lifetime risk for developing serious mental illnesses, such as major depressive disorder (MDD) (Danese & Baldwin, 2017; Mandelli, Petrelli, & Serretti, 2015), bipolar disorder (BD) (Agnew-Blais & Danese, 2016), post-traumatic stress disorder (Perry, 1994), schizophrenia (SCZ) (Varese et al., 2012), as well as personality disorders (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013) and substance use disorders (S. Huang et al., 2011). Research on subtypes of childhood trauma and early life stress reveal that physical abuse, sexual abuse, and neglect are associated with the development of mood disorders and anxiety disorders, while emotional abuse is associated with development of personality disorders and schizophrenia (Carr et al., 2013). Other studies have identified subtypes of emotional abuse and neglect to be among the most significant predictors of developing a mood disorder in adulthood (Mandelli et al., 2015). Experience of multiple childhood traumas is a significant predictor of increased chronicity of depression, increased suicidal behavior, as well as poor response to antidepressant or combined psychosocial and pharmacological treatment (Danese & Baldwin, 2017; Nanni, Uher, & Danese, 2012). History of childhood trauma is also highly prevalent in patients diagnosed with BD (Danese & Baldwin, 2017; Etain, Henry, Bellivier, Mathieu, & Leboyer, 2008). Incidence of childhood trauma is a significant predictor for severity of manic and depressive symptoms, psychotic symptoms, rapid cycling, greater number of depressive episodes, and increased risk of suicide attempts in individuals diagnosed with BD (Agnew-Blais & Danese, 2016; Daruy-Filho, Brietzke, Lafer, & Grassi-Oliveira, 2011; Leverich & Post, 2006)

1.2 Childhood Trauma and Risk for Psychosis

Importantly, childhood trauma has been reliably shown to be associated with increased risk for developing psychosis later in life (Stanton, Denietolis, Goodwin, & Dvir, 2020; Varese et al., 2012). Research on the relationship between childhood adversity and psychosis not only links childhood abuse and neglect to psychotic symptoms, specifically hallucinations, but also indicates that the relationship is causal, with a dose-effect (Baumeister, Lightman, & Pariante, 2014; Read, van Os, Morrison, & Ross, 2005). A large cohort study by (Croft et al., 2019), demonstrated that youth who experienced trauma in the first 17 years of life were 2.91 times more likely to have psychotic symptoms at 18 years of age, and those who experienced 3 or more types of childhood trauma were 4.7 times more likely to have psychotic symptoms. Exposure to trauma during childhood is associated with increased emotional and psychotic reactivity to stress in patients diagnosed with psychotic disorders (Lardinois, Lataster, Mengelers, Van Os, & Myin-Germeys, 2011). This increased stress reactivity may represent both an expressed genetic liability, as well as an acquired vulnerability due to exposure to traumatic events. Exposure to childhood trauma may actually sensitize patients with psychosis liability for the later exposure to daily life stress (Lardinois et al., 2011; Mondelli & Dazzan, 2019). In fact, Varese et al. (2012), argues the relationship between childhood trauma and psychosis is so significant, that removing childhood trauma from the population would yield a 33% decrease in number of individuals with psychosis.

1.3 Childhood Trauma and Inflammation

While studies have repeatedly shown that experience of childhood trauma is associated with an increased risk for developing both physical and mental illnesses later in life, the biological mechanisms by which this risk manifests are less explicit (De Bellis & Zisk, 2014). It

is known that early life experiences have a profound effect on the developing brain. Optimal development of some brain functions is actually experience-dependent, meaning that input from external stimuli during critical periods of neural development are essential for appropriate neurological development and absence of sufficient input can have deleterious effects (Takesian & Hensch, 2013). However, this dynamic and synergistic process, while critical for development, also leaves the developing brain vulnerable to influence by negative external stimuli.

Thus, the experience of stressful life events, such as childhood trauma, during critical periods of development has been shown to influence the development of neural systems, specifically those involved in response to stress/threat (McEwen, 2007). Yet, the experience of stress does not unequivocally lead to maladaptive consequences, as we know that not all individuals who experience childhood trauma go on to develop physical or mental illnesses. However, the experience of early life stress may uncover biological vulnerabilities in some individuals causing modulation of typical neurobiological stress response, creating life-long patterns of emotionality, behavioral, and physiological responding (McEwen, 2007). While this review will not discuss the role of epigenetics in development of mood disorders, it is important to briefly reference findings from animal model research which demonstrate that experience of early life stressful events, such as maternal separation or neglect, differentially affects neuronal development (Champagne et al., 2008), mRNA expression (Veenema, Reber, Selch, Obermeier, & Neumann, 2008) and even cortisol reactivity (Parr et al., 2012) due to differential expression of underlying epigenetic vulnerabilities (Klengel & Binder, 2015).

One neurological system is critical to the understanding of how environmental stimuli impact biological stress response: the hypothalamic-pituitary-adrenal (HPA) axis. The 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, McEwen, Gunnar, & Heim, 2009). Importantly, the HPA axis is highly responsive to environmental adversities both in childhood and in adulthood (Tsigos & Chrousos, 2002). Experience of early life stress is implicated in modulation of HPA-axis functioning (van Bodegom, Homberg, & Henckens, 2017), with experience of trauma affecting not only the expression of stress induced hormones (cortisol), but also increasing reactivity to acute stress, and decreasing recovery of cortisol following acute stress (Kuhlman, Geiss, Vargas, & Lopez-Duran, 2015). The responsiveness of the HPA-axis is determined by the ability of glucocorticoids to regulate the release of additional stress hormones, providing return to homeostasis once the perceived stress or threat has subsided (Lupien et al., 2009). 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, Newport, Bonsall, Miller, & Nemeroff, 2001; Heim et al., 2000; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Heim et al., 2002; Heim, Shugart, Craighead, & Nemeroff, 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 (studied independently), has led to the exploration of the role of the 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).

Research on the impact of childhood trauma on inflammation has established a dose-dependent relationship between number of childhood traumas and elevations/reductions in levels of many inflammatory markers, including IL-6 (Crosswell, Bower, & Ganz, 2014) and C-reactive protein (CRP)(Danese & McEwen, 2012; Lacey, Kumari, & McMunn, 2013; Slopen, Kubzansky, McLaughlin, & Koenen, 2013). Moreover, cytokines and other markers of inflammation are known to be potent activators of the central HPA-axis stress response (Chrousos, 1995; Turnbull & Rivier, 1995; Turnbull & Rivier, 1999). Inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β and interleukin-6 (IL-6) can stimulate the HPA-axis independently, or in combination (Chrousos, 1995; Tsigos et al., 1997). Further, IL-6 plays a major role in the immune stimulation of the HPA-axis, *particularly in times of chronic inflammatory stress* (Tsigos & Chrousos, 2002). Replicated studies have demonstrated that cytokines such as IL-1, IL-6, TNF-α and IFN-α, activate the HPA-axis by increasing levels of corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol (Grinevich et al., 2001; Rosenblat, Cha, Mansur, & McIntyre, 2014; Silverman, Miller, Biron, & Pearce, 2004; Turnbull & Rivier, 1995; Turnbull & Rivier, 1999). The influence of inflammation on the HPA-axis stress response is well-established (Beishuizen & Thijs, 2003; Brydon et al., 2009; McQuade & Young, 2000; Pace & Miller, 2009; Reichenberg et al., 2001). Thus, the HPA-axis is not only modulated by childhood trauma, but it is a powerful modulator of inflammatory activity, and is in turn modulated by inflammatory processes.

1.4 Inflammation and Risk for Psychopathology

Both inflammation and HPA-axis activation are mechanisms by which the body protects itself from threat. The immune system plays a critical role in the body's response to injury and infection as it simultaneously prevents the proliferation of pathogens, while also promoting

tissue survival, repair, and recovery through regulated circulation of inflammatory markers (Wärnberg, Gomez-Martinez, Romeo, Díaz, & Marcos, 2009). Relevant to the discussion of mood disorders, immune system response is associated with behavioral alterations in mood, sleep, energy, cognition, and motivation. Animal models provide evidence that induction of a "pro-inflammatory state" leads to patterns of behaviors in mice, termed "sickness behaviors" that resemble depressive symptomatology and include: lethargy, decreased appetite, decreased interest in exploring, decreased sexual activity, and increased time spent sleeping (Dunn, Swiergiel, & de Beaurepaire, 2005). In humans, increases in depressive symptoms (changes in mood, appetite, sleep, socialization, motivation, and memory) have been observed in conjunction with administration of immuno-therapies, such as vaccinations (Reichenberg et al., 2001), lipopolysaccharides (LPS; (Grigoleit et al., 2011), interferon (IFN; (Liang & Ghany, 2013), and interleukin-2 (IL-2; (Capuron, Ravaud, & Dantzer, 2000). Further, an increased prevalence of mood symptoms is present in a variety of inflammatory conditions including auto-immune diseases, cardiovascular diseases, diabetes, obesity, and metabolic syndrome, as well as benign inflammatory conditions including asthma and allergies (Brydon et al., 2009; Luppino et al., 2010). As a result of these associations, there has been an increased interest in exploring the relationship between inflammation and development of various forms of psychopathology.

Research on inflammation in individuals diagnosed with MDD has repeatedly shown increased incidence of mood symptoms and episodes associated with elevated levels of C-reactive protein (CRP), TNF-α, IL-1β, IL-2 and IL-6, in peripheral blood (Dowlati et al., 2010; Felger & Lotrich, 2013; Howren, Lamkin, & Suls, 2009; A. H. Miller, Maletic, & Raison, 2009; Valkanova, Ebmeier, & Allan, 2013). Further, increased severity of depressive symptoms has been associated with higher levels of inflammatory markers in a dose-dependent manner

(Howren et al., 2009). Similarly, research on inflammation in individuals diagnosed with BD has repeatedly shown increased incidence of mood symptoms and episodes associated with elevated levels of CRP, TNF-α, IL-1β, IL-2 and IL-6, and decreased BDNF (Boufidou, Nikolaou, Alevizos, Liappas, & Christodoulou, 2004; Brietzke et al., 2009; Dickerson, Stallings, Origoni, Boronow, & Yolken, 2007; Goldstein et al., 2011; Goldstein, Kemp, Soczynska, & McIntyre, 2009; T. L. Huang & Lin, 2007; Munkholm, Brauner, Kessing, & Vinberg, 2013). Acute elevations in inflammatory markers have also been shown to occur during depressive and manic episodes, with marker concentrations peaking during mood episodes and dropping during euthymic periods (Boufidou et al., 2004; Brietzke et al., 2009).

1.5 Inflammation and Psychosis

Clinical High Risk. Impairment of HPA-axis functioning has been shown to occur within the CHR population (Thompson et. al, 2007). A limited number of studies have explored differences in levels of plasma 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. Finally, Yee, Lee, and Lee (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.

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 finding are specific to psychosis risk or general psychopathology and environmental factors.

First Episode Psychosis. Although research on levels of inflammatory plasma analytes in FEP subjects has been more prolific, it is also more inconsistent. A recent systematic review (Schiavone & 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 were not consistent across studies, with additional evidence from several studies demonstrating these findings only in drug naive subjects, no significant differences or suppression of analytes (IL-6, IL-2, IL-4, IL-10, TNF-α, and IL-17) in FEP compared to HC subjects (Schiavone & Trabace, 2017). As will be discussed, 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 & Mane, 2015). Importantly, Toll and Mane (2015) discuss that studies reporting reductions in FEP levels of BDNF compared to HC subjects have been predominantly conducted in drug-naïve FEP patients as compared to studies reporting no alterations in FEP levels of BDNF compared to HC subjects have been conducted in medicated patients. These results are consistent with previous meta-analyses in drug-naïve schizophrenia groups (Green, Matheson, Shepherd, Weickert, & Carr, 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, Gencoglan, Yuksel, Kaplan, & Aktas, 2015).

Despite inconsistent findings, several studies (Chan et al., 2015; Perkins et al., 2015; Schwarz et al., 2012; Schwarz et al., 2014) have demonstrated the clinical relevance of inflammatory plasma analytes in psychosis groups, through successful 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. 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.

Clinical Relevance of Inflammation and Childhood Trauma. Associations between inflammatory plasma analytes, psychotic symptoms severity, and functioning has been well studied in patients with chronic psychosis (Hong et al., 2017; Lee, Hong, Martin, Eyler, & Jeste, 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, plasma 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).

Very few studies have evaluated the effect of childhood trauma on inflammation in psychosis. In a sample of individuals with chronic schizophrenia subjects, Dennison, McKernan, Cryan, and Dinan (2012) provide evidence that individuals with a history of childhood trauma show significantly higher levels of TNF-a and IL-6 as compared to subjects without a history of trauma and healthy controls. In fact, both Dennison et al. (2012) and Di Nicola et al. (2013) demonstrated that levels of TNF-a were correlated with history of childhood trauma, specifically

severity of the trauma in psychosis subjects. Hepgul et al. (2012), reports that levels of CRP were significantly higher in first episode psychosis subjects with a history of childhood trauma as compared to those without a history of childhood trauma and healthy controls. Chase et al. (2019) demonstrated that childhood trauma, through its effects on IL6, may be a risk factor for schizophrenia. This is consistent with the meta-analysis conducted by Baumeister, Akhtar, Ciufolini, Pariante, and Mondelli (2016), demonstrating that CRP, IL-6, and TNF-a were markedly elevated in individuals with a history of childhood trauma versus those without. Finally, Mondelli et al. (2010) conducted research on cortisol awakening response in first episode psychosis and established that history of childhood sexual trauma is associated with blunted cortisol awakening response. Authors purport that this finding helps to explain the association between HPA-axis abnormalities and excess psychological stress in first episode psychosis subjects. Importantly, no studies to our knowledge have sought to examine the relationship between childhood trauma, inflammation, and clinical outcomes in CHR subjects.

Findings from North American Prodrome Longitudinal Study 2 (NAPLS2).

However, results from the North American Prodrome Longitudinal Study (NAPLS) 2 have established several important findings regarding the relationship between childhood trauma and inflammation *independently* on clinical outcomes in CHR subjects. Firstly, Addington et al. (2013) evaluated the relationship between childhood trauma and clinical outcomes in CHR subjects. It was demonstrated that individuals at CHR report significantly more trauma and bullying than healthy controls. Further, those CHR subjects who experienced past trauma and bullying are more likely to have increased levels of depression and anxiety and a poorer sense of self. Importantly, higher levels of total childhood trauma were demonstrated to be associated with lower global role functioning (Addington et al., 2013).

Second, 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, confirming that inflammation, oxidative stress, and dysregulation of hypothalamic-pituitary axes may be prominent in the earliest stages of psychosis (Perkins et al., 2015). The classifier included 15 analytes (selected from 117), demonstrating that unique profiles of inflammatory plasma analytes can be used to differentiate between patient and control groups.

Finally, Walker et al. (2013) demonstrated evidence of heightened cortisol secretion in CHR individuals also indicating nonspecific associations between cortisol levels and symptom severity, as well as symptom progression. Thus, adding to accumulating evidence regarding role of HPA activity in prediction of conversion to psychosis. However, despite these relevant discoveries, it has yet to be determined whether inflammation may serve as a biological mediator between childhood trauma and CHR clinical outcomes (psychosis risk symptom severity and functioning).

1.6 Purpose and Specific Aims

A robust body of literature supports the hypothesis that exposure to early life stress, such as childhood trauma, may uncover genetic and epigenetic vulnerabilities that influence neurobiological responses to stress, including activation of the HPA-axis and associated immune system response. Further, individuals diagnosed with psychosis have a higher prevalence of exposure to childhood trauma, as well as evidence of inflammatory dysregulation. It is therefore reasonable to suggest that experience of maltreatment in childhood may lead to changes in neurobiological response to stress, as measured by markers of inflammation, and that this response is associated with the onset of various mental illnesses in adulthood, including

psychosis. However, to our knowledge, no studies to date have evaluated the relationships between childhood trauma, inflammation, and clinical outcomes in individuals at clinical high risk for psychosis. Thus, the research question that guided this study is as follows: *Is a history of childhood trauma linked to a pro-inflammatory phenotype in individuals at clinical high risk for psychosis?*

Aim 1. Evaluate group differences in experience of childhood trauma, psychosis-risk symptom severity, functioning, and levels of inflammatory analytes between youth at CHR and UC subjects. ***Hypothesis 1a.*** CHR subjects will demonstrate higher levels of inflammatory anaytes known to be associated with experience of childhood trauma (Cortisol, CRP, IL-6, and TNF-α, as well as the 15-Analyte Index developed by Perkins et. al (2015)) relative to UC subjects (**Table 1**). ***Hypothesis 1b.*** CHR subjects will demonstrate higher total number of unique trauma, higher levels of baseline psychosis-risk symptom severity, and lower baseline global/social/role functioning relative to UC subjects. ***Hypothesis 1c.*** CHR subjects who experienced history of childhood trauma (CHR_{Trauma}) will demonstrate higher levels of inflammatory analytes known to be associated with experience of childhood trauma (Cortisol, CRP, IL-6, and TNF-α, as well as the 15-Analyte Index developed by Perkins et. al (2015)), higher levels of baseline psychosis symptom severity, and lower baseline global/social/role functioning relative to CHR subjects with no history of childhood trauma ($CHR_{NoTrauma}$).

Table 1. A-priori identified blood based inflammatory analytes.

Perkins et al., (2015) 15 Analyte Z-Score Index	Additional Analytes per Literature Review
Malondialdehyde- Modified Low-Density Lipoprotein (MDA-LDL)	Cortisol*
Thyroid Stimulating Hormone (TSHB)	Interleukin-6 (IL-6)
Interleukin-1 beta (IL1-β)*	C-Reactive Protein (CRP)
Matrix Metalloproteinase 7 (MMP7)	Tumor Necrosis Factor-alpha (TNF-α)
Immunoglobulin E (IGHE)	
Uromodulin (UMOD)	
Growth Hormone (GH1)	
Apolipoprotein D (APOD)	
KIT ligand (KITLG)	
Cortisol*	
Factor VII (F7)	
Interleukin-7 (IL7)	
Interleukin-8 (IL8)	
Resistin (RETN)	

* Indicates markers overlapping between literature review and 15-Analyte Index.

Aim 2. Determine whether highly correlated networks of inflammatory markers can be identified using factor analysis. ***Hypothesis 2a*****.** Highly correlated networks of inflammatory markers will be identified.

Aim 3. Examine the relationship between inflammation, childhood trauma, psychosis risk symptom severity, and functioning in CHR subjects. ***Hypothesis 3a*****.** There will be a significant positive relationship between childhood trauma and psychosis risk symptom severity and a significant negative relationship between childhood trauma and global/social/role functioning for CHR subjects. ***Hypothesis 3b.*** There will be a significant positive relationship between inflammatory analytes, childhood trauma, and psychosis risk symptom severity, as well as a significant negative relationship between inflammatory analytes and global/social/role functioning in CHR subjects. ***Hypothesis 3c*****.** Inflammation will partially mediate the relationship between childhood trauma and psychosis-risk symptom severity, as well as between childhood trauma and functioning in CHR youth.

Exploratory Aim. Explore the effect of psychosis-risk conversion status and trauma history on inflammation, psychosis risk symptom severity, and functioning in CHR subjects.

2. METHODS

2.1 Participants

Data for this project was derived from The North American Prodrome Longitudinal Study (NAPLS 2), an 8-site observational study of the predictors and mechanisms of conversion to psychosis in persons meeting the Criteria of Prodromal States (COPS) (Addington et al., 2015). The overall NAPLS 2 cohort included 765 clinical high-risk and 280 demographically similar unaffected comparison (UC) subjects aged between 12 and 35. The study was approved by the Institutional Review Board at each site, and each subject provided written informed consent or assent, with a parent or guardian also consenting for minor subjects. The plasma analysis for biomarkers included a smaller subset of this larger subject pool. This subsample differs from the larger NAPLS sample in that a higher proportion of CHR subjects included are known to have progressed to psychosis (44%; CHR-C, n = 29), whereas the remaining CHR subjects had been followed 2 years and not progressed to psychosis during that time (CHR-NC, n = 38). The unaffected comparison subjects (UC, n = 34) did not meet CHR criteria or have a history of a psychotic disorder and were chosen to be demographically similar to the CHR subjects.

2.2 Participant Characterization and Inclusion Criteria/Exclusion Criteria.

Individuals at CHR had to be between 12 and 35 years old and meet diagnostic criteria for a prodromal syndrome as per the COPS criteria(T. J. Miller et al., 2003) or if under 19, meet criteria for schizotypal personality disorder (SPD). Control subjects could not meet criteria for any prodromal syndrome, any current or past psychotic disorder or a Cluster A personality

disorder diagnosis and could not have a family history (in first-degree relatives) of any psychotic disorder or any other disorder involving psychotic symptoms. UC subjects could not be currently using psychotropic medication. Participants were excluded if they met criteria for current or lifetime Axis I psychotic disorder, including affective psychoses, IQ < 70, or had a history of a central nervous system disorder, substance dependence in the past 6 months, or if the diagnostic prodromal symptoms were clearly caused by an Axis I disorder. Other non-psychotic DSM-IV disorders were not exclusionary (e.g., substance abuse disorder, major depression, anxiety disorders, Axis II disorders), as long as the disorder did not account for the individual's prodromal symptoms. Use of antipsychotics was not an exclusion provided there was clear evidence that prodromal (but not psychotic) symptoms were present when the medication was started.

2.3 Clinical Assessment

Diagnostic Assessment. The SCID (First, Spitzer, Gibbon, & Williams, 2002) was used to rule out the presence of psychosis. The SIPS and the SOPS were used to assess COPS criteria and severity of attenuated positive symptoms and negative symptoms (T. J. Miller et al., 2003).

The SOPS is a 19-item scale designed to measure the severity of prodromal symptoms. The SOPS contains four subscales for Positive, Negative, Disorganization and General Symptoms. The five positive symptoms are P1-unusual thought content/delusional ideas, P2-suspiciousness/persecutory ideas, P3-grandiose ideas, P4-perceptual abnormalities, P5-disorganized communication. The six negative symptoms are N1-social anhedonia, N2-avolition, N3-expression of emotion, N4-experience of emotion and self, N5-ideational richness, N6-occupational functioning. The four disorganization symptoms are D1-odd behavior or appearance, D2-bizarre thinking, D3- trouble with focus and attention, D4-impairment in

personal hygiene. The four general symptoms are G1-sleep disturbance, G2-dysphoric mood, G3-motor disturbances, G4-impaired tolerance to normal stress. Positive symptoms are rated on a scale from 0 (absent) to 6 (severe/psychotic). Negative, disorganized, and general symptoms are rated on a scale from 0 (absent) to 6 (extreme). All clinical evaluations were completed by staff with extensive training in clinical interviewing and certified in administering the SIPS assessments after achieving good to excellent inter-rater reliability (intraclass correlation SOPS symptom ratings > 0.75 for SOPS symptom ratings).

Clinical outcome at each follow-up assessment was determined in the following way: (i) remission (remission from all syndromes which means scores of 2 or less on all five positive symptoms on the SOPS scale, or for those who have only GRD, "in remission" will require GAF to have returned to 90% of previous best GAF.); (ii) symptomatic (not currently meeting criteria for a prodromal risk syndrome but having ratings of 3-5 on any one of the five positive symptoms on the SOPS, or with the no change in the GAF); (iii) prodromal progression (currently meeting criteria for one of the at risk syndromes; APSS, GRD, BIPS) and (iv) psychotic (currently meeting criteria for a psychotic disorder or evidencing scores of 6 on one or more positive symptoms of the SOPS).

Transition to psychosis was determined by meeting the Presence of Psychotic Symptoms (POPS) criteria. Transition criteria is that at least one of the five SOPS positive symptoms reached a psychotic level of intensity (rated 6) for a frequency of ≥ 1 hour per day for 4 days per week during the past month or that symptom seriously impacted functioning (e.g., severely disorganized, or dangerous to self or others).

Functioning. Functioning was assessed with the Global Functioning Scales: Social and Role (GF:S & GF:R) (Auther, Smith, & Cornblatt, 2006; Niendam, Bearden, Johnson, &

Cannon, 2006). Both scales range from 1 (severely impaired) to 10 (superior functioning). All functional evaluations were completed by staff with extensive training in clinical interviewing and certified in administering the GFR and GFS after achieving good to excellent inter-rater reliability (interclass correlation GFS >0.944; interclass correlation GFR >0.913).

Childhood Trauma History. Experience of trauma was assessed using the Childhood Trauma and Abuse Scale, a semi-structured interview used to detect the occurrence of psychological bullying, physical bullying, emotional neglect, physical abuse, psychological abuse, or sexual abuse, before the age of 16. This form was modeled from the Childhood Trauma Questionnaire, but did not include measure of severity or chronicity of trauma subtype (Bernstein et al., 1997).

2.4 Biological Inflammatory Marker Assessment

Plasma collection and assay. Plasma analysis reported here was conducted in March 2012. Plasma Collection Blood samples used in this analysis were drawn at the baseline visit in Becton Dickenson P100 blood collection tubes with ethylene diamine tetra-acetic acid as anticoagulant, proprietary protein stabilizers, and a mechanical separator. All samples were processed within 120 minutes (mean time to freezer = 28 minutes, SD = 2 minutes) and stored at −80°C until analysis. Plasma Assay Plasma samples were sent on dry ice to Myriad Rules Based Medicine, a biomarker testing laboratory that has maintained clinical laboratory improvement amendments accreditation by the Commission on Office Laboratory Accreditation since 2006.

Samples were analyzed with the Human Discovery Map assay, a Luminex bead-based multiplex immunoassay that included 185 analytes involved in hormonal responses, inflammation, growth, oxidative stress, and metabolism, all according to Rules-Based Medicine

standard operating procedures. Technicians ran assays without knowledge of clinical status of the subjects.

Exclusion of analytes and normalization of analyte data. Procedures for exclusion of normalization of data were completed in a prior study (Perkins et al., 2015). The assay included 185 analytes. Twenty-three analytes were excluded as they were not detected in ≥ 20% of the subjects, thus yielding a total of 117 remaining analytes. The normal plasma concentrations varied analyte-to analyte up to 1,000,000-fold. So those results could be viewed on the same scale, each analyte was standardized (z score) to the average and SD values of the UC subjects (see Perkins et al. (2015) for details on z-score correction and normalization of data).

15-Analyte Z-Score Index. (Perkins et al., 2015) developed a 15-Analyte Index that distinguished persons at CHR who developed psychosis from those that did not, as well as unaffected control subjects. The index was derived using a "greedy algorithm" that selected 15 analytes (from 117), with an area under the receiver operating curve for CHR-P vs UC of 0.91 and CHR-P vs CHR-NP of 0.88. Subsequently, randomly scrambled group membership followed by reconstructions of the entire classifier method yielded consistently weak classifiers, indicating that the true classifier is highly unlikely to be a chance occurrence and demonstrating that unique profiles of inflammatory plasma analytes can be used to differentiate between patient and control groups (see Perkins et al. (2015)for full details on 15-Analyte Index development).

2.5 Statistical Analyses

Hypothesis 1a. *CHR subjects will demonstrate higher levels of inflammatory anaytes known to be associated with experience of childhood trauma (Cortisol, CRP, IL-6, and TNF-α, as well as the 15-Analyte Index developed by Perkins et. al (2015)) relative to UC subjects (**Table 1**).* ***Hypothesis 1b.*** *CHR subjects will demonstrate higher total number of unique trauma,*

higher levels of baseline psychosis-risk symptom severity, and lower baseline global/social/role functioning relative to UC subjects. ***Hypothesis 1c.*** *CHR subjects who experienced history of childhood trauma (CHR_{Trauma}) will demonstrate higher levels of inflammatory analytes known to be associated with experience of childhood trauma (Cortisol, CRP, IL-6, and TNF-α, as well as the 15-Analyte Index developed by Perkins et. al (2015)), higher levels of baseline psychosis symptom severity, and lower baseline global/social/role functioning relative to CHR subjects with no history of childhood trauma ($CHR_{NoTrauma}$).* Independent samples t-test and Chi-squared tests were used to evaluate group differences between UC and CHR subjects, as well as between CHR_{Trauma} and $CHR_{NoTrauma}$ groups, in psychosis symptom severity, global, social and role functioning, as well as inflammatory markers.

Hypothesis 2a. *Highly correlated networks of inflammatory markers will be identified.* Exploratory Factor Analysis (EFA) was used to explore whether highly correlated networks of inflammatory markers could be identified from the 117 analytes in the present study. EFA was chosen over Confirmatory Factor Analysis (CFA), as there is no defined theory regarding the number of factors or which factors theories might best fit an a-priori model of inflammatory networks. In order to limit the potential subjectiveness of EFA, we completed a systematic application of theoretical principles to latent variables, factor reduction, and construction (Williams, Onsman, & Brown, 2010).

Firstly, the data was analyzed to determine suitability for factor analysis. A correlation matrix will be used to display the relationships between variables for inspection of correlation coefficients over 0.3. Hair J, Anderson RE, Tatham RL, and WC. (1995) categorized these loadings using another rule of thumb as ±0.30=minimal, ±0.40=important, and ±.50=practically significant. If no correlations go beyond 0.30, then factor analysis will be reconsidered, only

inflammatory markers known to be associated with childhood trauma from existing research will be used in subsequent analyses. Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy (H.F. Kaiser, 1970, 1974) and Bartlett's Test of Sphericity (Bartlett, 1950) was used to assess the suitability of the respondent data for factor analysis. The KMO index is recommended when the cases to variable ratio is less than 1:5. The KMO index ranges from 0 to 1, with 0.50 considered suitable for factor analysis (Hair J et al., 1995; Tabachnick & Fidell, 2007). Further, the Bartlett's Test of Sphericity should be significant ($p<.05$) for factor analysis to be suitable to utilize (Bartlett, 1950).

If the data is not suitable for factorability analyses, EFA will stop after this step and a-priori identified analytes, including Perkins et al. (2015) 15-Analyte Index will be used in subsequent correlation and mediation analyses. Otherwise, principal components analysis (PCA) will be used to extract factors as no priori theory or model exists to guide this analysis (Gorsuch, 1983). Thirdly, multiple extraction techniques will be used for factor extraction including: Kaiser's criteria for eigenvalue's > 1 (H. F. Kaiser, 1960), the Scree plot test (Cattell, 1966), and parallel analysis (Horn, 1965). Each of these tests will be performed and extracted factors evaluated to determine the most consistent and parsimonious number of factors. Fourthly, factor rotation will be used in order to maximize high item loadings and minimize low item loadings, therefore producing a more interpretable and simplified solution (Williams et al., 2010). Although there are two common rotation techniques: orthogonal rotation and oblique rotation, oblique rotation will be used in order to account for factor correlations, which is more accurate for research involving human behaviors and preferred when data does not meet priori assumptions (Costello & Osborne, 2005). Finally, factors will be labeled. The labelling of factors is a subjective, theoretical, and inductive process (Pett, Lackey, & Sullivan, 2003). Factors will

be operationalized and descriptively labelled according to constructs that reflect theoretical concepts in inflammatory research.

Hypothesis 3a. *There will be a significant positive relationship between childhood trauma and psychosis risk symptom severity and a significant negative relationship between childhood trauma and global/social/role functioning for CHR subjects.* ***Hypothesis 3b.*** *There will be a significant positive relationship between inflammatory analytes, childhood trauma, and psychosis risk symptom severity, as well as a significant negative relationship between inflammatory analytes and global/social/role functioning in CHR subjects.* Partial Pearson product correlation analyses were used to evaluate the relationships between total trauma, inflammatory analytes, SOPS, GAF, GFR, and GF. Differences in demographic variables, substance use, psychotropic medication, and blood sampling time were controlled for in analyses.

Hypothesis 3c. *Inflammation will partially mediate the relationship between childhood trauma and psychosis-risk symptom severity, as well as between childhood trauma and functioning.* Mediators can be defined as mechanisms through which one variable might achieve its effects. The 3-step Baron and Kenny (1986) mediation analysis was conducted to determine if the mediator (inflammation) is caused by the initial IV (childhood trauma) and is a cause of the DV (clinical outcome), the initial IV (childhood trauma) loses its significance once the mediator (inflammation) is included in the model. More explicitly, first, simple linear regression was used to confirm the relationship between the independent variable, total childhood trauma, and the dependent variable, psychosis risk symptom severity OR functioning. Second, simple linear regression was used to confirm the relationship of childhood trauma and inflammatory analytes defined in Hypothesis 2a and 3b. Third, a final linear regression was used to confirm the

significance of the relationship between the inflammatory analytes and psychosis risk symptom severity, or functioning in the presence of childhood trauma, as well as confirm the insignificance (or the meaningful reduction in effect) or the relationship between the childhood trauma, psychosis risk symptom severity (OR functioning), in the presence of the mediator (inflammatory analyte). Significant associations from hypotheses 3a and 3b will be used to determine the most reasonable clinical outcomes (psychosis risk symptom severity and functioning variables) to be used as dependent variables (DV) and inflammatory analytes to be used as mediators (M) in subsequent models.

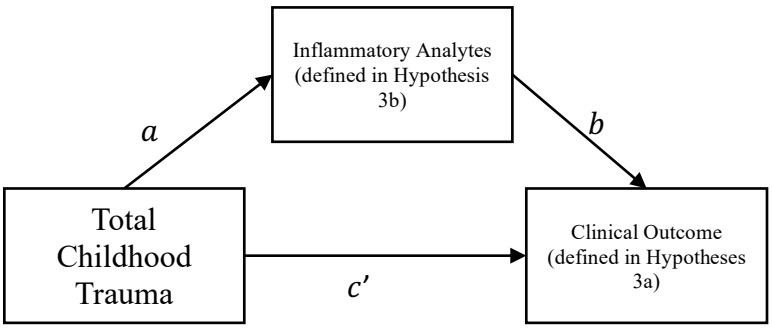


Figure 1. A Potential Mediation Model

Exploratory analyses. Multivariate Analysis of Covariance (MANCOVA) with Bonferroni Post Hoc Testing ($p< 0.05$)and Chi-squared tests were used to explore the between-subjects effects of conversion status (groups: CHR-C and CHR-NC) and trauma history (groups: CHR-t and CHR-nt) on clinical, functional, and inflammatory analytes. Homogeneity assumptions were evaluated at an alpha level of .001 using Box's M test of homogeneity of covariance and Levene's homogeneity test. Wilk's criterion (Λ) was used as the omnibus test statistic.

3. Results

3.1 Participant Characteristics

Demographic characteristics for CHR and UC groups are listed in **Table 2**. Independent samples t-test and Chi-squared tests revealed UC and CHR groups did not differ in age, gender, or ancestry and no significant differences were observed for elapsed blood sample storage time or time of day that blood draw occurred. Groups significantly differed in proportion of substance and medication use. CHR were more likely than UC subjects to use tobacco (χ^2 (2, N= 101)=8.39, p<0.001) and cannabis (χ^2 (2, N=101)=5.05, p= 0.03), as well as be prescribed antipsychotic (χ^2 (2, N=101)=8.25, p= 0.04) and antidepressant medication (χ^2 (2, N=101)=7.75, p= 0.05) at the time of sampling. CHR_{Trauma} and $CHR_{NoTrauma}$ groups also did not differ in age, gender, or ancestry and no significant differences were observed for elapsed blood sample storage time or time of day that blood draw occurred.

Table 2. Demographic characteristics (N = 101)

Demographics	Total N= 101	UC n= 34	CHR n= 67	F or χ^2	*t(99)*	*p*-value	Cohen's *d* or Cramer's *V*
Age, mean (SD)	19.6 (4.3)	19.9 (4.5)	19.5 (4.3)	0.03	0.5	0.88	0.09
Gender No. (%)							
Male	66 (65.3%)	22 (64.7%)	44 (65.7%)	0.01	-	0.92	0.01
Female	35 (34.7%)	12 (35.3%)	23 (34.3%)				
Ancestry, No. (%)							
Asian	17 (16.8%)	3 (8.8%)	14 (20.9%)				
African	24 (23.8%)	11 (32.4%)	13 (19.4%)	3.54	-	0.17	0.19
Caucasian	60 (59.4%)	20 (58.8%)	40 (59.7%)				
Medications, No. (%)							
antipsychotic	14 (13.9%)	0 (0%)	14 (20.9%)	8.25	-	0.04*	0.29
antidepressant	18 (17.8%	1 (2.9%)	17 (25.4%)	7.75	-	0.05*	0.28
stimulant	4 (4%)	0 (0%)	4 (6.0%)	2.11	-	0.15	0.15
mood stabilizer	3 (3%)	0 (0%)	3 (4.5%)	1.57	-	0.21	0.13
benzodiazepine	5 (5%)	0 (0%)	5 (7.5%)	2.67	-	0.10	0.16
Substance Use, No. (%)							
Tobacco	27 (26.7%)	3 (8.8%)	24 (35.8%)	8.39	-	p<0.01*	0.29
Cannabis	22 (21.8%)	3 (8.8%)	19 (28.4%)	5.05	-	0.03*	0.22
Alcohol	44 (43.6%)	16 (47.1%)	28 (41.8%)	0.26	-	0.61	0.05
Labs, mean (SD)							
Time of Blood Draw	12.4 (1.9)	12.3 (1.8)	12.4 (1.9)	0.19	-0.4	0.66	-0.05
Bloodwork elapsed time (minutes)	26.9 (15.7)	27.1 (19.2)	26.8 (13.8)	3.45	0.1	0.07	0.01

3.2 Group Differences in Clinical Variables: Childhood Trauma, Psychosis Risk Symptoms, Functioning, and Inflammatory Analytes

Childhood Trauma. Independent samples t-tests and Chi-squared tests revealed significant group differences between UC and CHR subjects in total number of unique childhood traumas experienced as well as group differences in occurrence of each trauma subtype (**Table 3**). On average, CHR subjects reported experiencing at least 2 different subtypes of unique childhood trauma (*M*= 2.2, *SD*= 1.8), while UC subjects reported experiencing less than 1 subtype of trauma (*M*= 0.6, *SD*= 1.0, *t*(99)= -4.8, *p*<0.001, *d*= -1.1). Further, CHR subjects were more likely than UC subjects to endorse history of any subtype of childhood trauma (χ^2 (2, *N*=

101)= 12.73, $p< 0.001$, $v= 0.36$), with 75% of CHR subjects endorsing a history of any childhood trauma subtype as compared to 40% of UC subjects. CHR were more likely than UC subjects to report history of every trauma subtype except sexual abuse (i.e. higher incidence of psychological bullying (χ^2 (2, $N= 101$)= 8.59, $p< 0.001$, $v= 0.29$), physical bullying (χ^2 (2, $N=101$)= 5.86, $p= 0.02$, $v= 0.24$), emotional neglect (χ^2 (2, $N= 101$)= 15.8, $p< 0.001$, $v= 0.40$), psychological abuse (χ^2 (2, $N= 101$)= 14.8, $p< 0.001$, $v= 0.38$), and physical abuse (χ^2 (2, $N= 101$)= 8.45, $p< 0.001$, $v= 0.29$).

Of the 13 UC subjects that endorsed history of childhood trauma, 100% endorsed psychological bullying, 30% endorsed physical bullying, 1.5% endorsed emotional neglect, less than 1% endorsed psychological or physical abuse, and 0% endorsed sexual abuse. Of the 50 CHR subjects that endorsed history of childhood trauma, 92% endorsed psychological bullying, 60% endorsed emotional neglect, 52% endorsed psychological abuse, 46% endorsed physical bullying, 36% endorsed physical abuse, and 1% endorsed sexual abuse. Thus, while the most frequent trauma subtype endorsed by UC and CHR subjects was psychological bullying, the next most frequently endorsed trauma subtype for CHR subjects was emotional neglect compared to physical bullying for UC subjects.

Clinical Variables. CHR subjects demonstrated significantly higher scores on all domains of the SOPS, including total score, positive symptoms, negative symptoms, disorganized symptoms, and general symptoms as compared to UC subjects. CHR subjects also demonstrated significantly lower scores on all functional assessments, including lower GAF, GFS, and GFR, as compared to UC subjects. Finally, while UC and CHR subjects did not differ in total number of stressful life events endorsed, CHR subjects reported a significantly higher subjective experience of stress ($M= 111.6$,SD= 88.1) associated with life events as compared to

UC subjects (M= 61.6,SD= 41.0, t(99), p=0.02, d= 0.73). No group differences were observed between UC and CHR subjects for self-reported daily life stress.

Inflammatory Analytes. CHR subjects demonstrated significantly lower z-score corrected levels of TNF-α (M= -0.139, SD= 0.5) as compared to UC subjects (M= 0.013,SD= 1.0, t(99), p= 0.0, d= 0.19). However, no group differences were observed in z-score corrected levels of the 15-Analyte Index, Cortisol, CRP, or IL-6.

Table 3. Independent samples t-test exploring group differences between CHR and UC subjects in history of childhood trauma, psychosis risk symptoms, functioning, and inflammatory analytes.

Clinical Measure	Total N=101	UC n=34	CHR n=67	F or χ^2	*t(99)*	*p*-value	Cohen's *d* or Cramer's *V*
Childhood Trauma, mean (SD) and No.(%)							
Total number childhood trauma	1.7 (1.7)	0.6 (1.0)	2.2 (1.8)	20.8	-4.8	p<0.001*	-1.1
Any subtype of childhood trauma	63 (62.4%)	13 (38.2%)	50 (74.6%)	12.73	-	p<0.001*	0.36
Psychological bullying	59 (58.4%)	13 (38.2%)	46 (68.7%)	8.59	-	p<0.001*	0.29
Physical bullying	27 (26.7%)	4 (11.8%)	23 (34.3%)	5.86	-	p=0.02*	0.24
Emotional Neglect	32 (31.7%)	2 (5.9%)	30 (44.8%)	15.8	-	p<0.001*	0.40
Psychological Abuse	27 (26.7%)	1 (2.9%)	26 (38.8%)	14.8	-	p<0.001*	0.38
Physical Abuse	19 (18.8%)	1 (2.9%)	18 (26.9%)	8.45	-	p<0.001*	0.29
Sexual Abuse	5 (5%)	0 (0%)	5 (5%)	2.67	-	p=0.10	0.16
Psychosis Risk Symptoms, mean (SD)							
SOPS Total	22.2 (16.1)	3.7 (3.9)	31.6 (11.1)	21.64	-14.2	p<0.001*	-3.35
Positive Symptoms	9.5 (6.7)	1.5 (1.8)	13.5 (4.1)	12.37	-16.0	p<0.001*	-3.79
Negative Symptoms	8.7 (7.5)	1.3 (1.7)	12.6 (6.3)	30.57	-10.2	p<0.001*	-2.45
Disorganized Symptoms	4.1 (3.6)	0.9 (1.2)	5.8 (3.4)	23.30	-8.1	p<0.001*	-1.92
General Symptoms	6.6 (5.4)	1.5 (1.8)	9.2 (4.7)	22.01	-9.3	p<0.001*	-2.16
Functioning, mean (SD)							
GAF	59.8 (20.4)	85.0 (7.5)	47.1(10.6)	5.93	18.6	p=0.02*	4.13
GFS	7.2 (2.0)	9.0 (0.9)	6.3 (1.7)	14.34	8.8	p<0.001*	1.99
GFR	6.9 (2.3)	8.7 (0.9)	5.9 (2.2)	19.19	6.8	p<0.001*	1.67
Inflammatory Analytes, mean (SD)							
15-Analyte Index	2.846 (5.1)	0.139 (4.7)	4.219 (4.8)	0.00	-4.1	p=0.99	-0.86
Cortisol	0.169 (1.5)	0.001 (1.0)	0.254 (1.7)	1.14	-0.8	p=0.29	-1.82
CRP	0.072(1.03)	0.004 (1.0)	0.106 (1.0)	1.12	-0.5	p=0.29	-0.10
IL-6	0.317(1.15)	0.017 (1.0)	0.470 (1.2)	2.20	-1.9	p=0.14	-0.41
TNF-α	-0.088 (0.7)	0.013 (1.0)	-0.139 (0.5)	7.49	1.0	p=0.01*	0.19

Group Differences in Trauma History. As seen in **Table 4**, Independent samples t-test revealed no significant overall group differences between CHR_{Trauma} and $CHR_{NoTrauma}$ subjects in SOPS (all domains), GAF, GFR,, the 15-Analyte Index, Cortisol, CRP, TNF-α, or IL-6.

However, when analyzing differences between subtype of childhood trauma in inflammation, psychosis risk symptom severity, and functioning, it was revealed that CHR

subjects who endorsed history of psychological bullying demonstrated significantly lower levels of Cortisol (M= 0.097, SD= 1.00) as compared to CHR subjects who did not (M= 0.600, SD= 2.57, p=0.02, *d*= -0.26; no significant differences in SOPS, GAF, GFS, GFR, the 15-Analyte Index, CRP, TNF-α, or IL-6). Further, when evaluating differences in total trauma history, independent samples t-test showed that individuals who endorsed history of psychological bullying (M= 3.02, SD= 1.44), physical abuse (M= 4.27, SD= 0.89), and sexual abuse (M= 5.0, SD= 0.71) demonstrated significantly greater total trauma endorsed as compared to those who did not report each of those trauma subtypes (Psychological Bullying: M= 0.43, SD= 0.97, p=0.01, *d*= 2.11; Physical abuse: M= 1.45, SD= 1.37, p=0.01, *d*= 2.44; Sexual Abuse: M= 1.98, SD= 1.64, p=0.01, *d*= 2.39). Significant group differences in inflammation, psychosis risk symptoms, and functioning, were not observed for CHR subjects that endorsed history of physical bullying, emotional neglect, psychological abuse, or sexual abuse, as compared to CHR subjects with no history of that trauma subtype.

Table 4. Independent samples t-test exploring group differences between CHR-T and CHR-NT subjects in history of psychosis risk symptoms, functioning, and inflammatory analytes.

Clinical Measure	Total N=67	CHR-NT n=17	CHR-T n=50	F	*t(65)*	*p*-value	Cohen's *d*
Psychosis Risk Symptoms, mean (SD)							
SOPS Total	31.6(11.1)	32.6(10.9)	31.2 (11.2)	0.03	0.44	0.85	0.13
Positive Symptoms	13.5 (4.1)	12.4 (3.3)	13.9 (4.4)	1.28	-1.33	0.26	-0.39
Negative Symptoms	12.6 (6.3)	14.2 (7.5)	12.0 (5.8)	2.59	1.29	0.11	0.32
Disorganized Symptoms	5.8 (3.4)	6.0 (3.4)	5.7 (3.4)	0.85	0.30	0.36	0.09
General Symptoms	9.2 (4.7)	8.0 (4.6)	9.6 (4.7)	0.16	-1.25	0.69	-0.34
Functioning, mean (SD)							
GAF	47.1(10.6)	50.1(10.8)	46.0 (10.4)	0.11	1.39	0.75	0.39
GFS	6.3 (1.7)	6.4 (1.9)	6.2 (1.6)	1.91	-0.64	0.17	0.11
GFR	5.9 (2.2)	5.63 (2.6)	6.0 (2.1)	0.18	0.32	0.67	-0.16
Inflammatory Analytes, mean (SD)							
15-Analyte Index	4.219 (4.8)	4.999(5.6)	3.955 (4.5)	1.17	0.77	0.28	0.21
Cortisol	0.254 (1.7)	0.413 (2.3)	0.201 (1.4)	3.13	0.45	0.08	0.11
CRP	0.106 (1.0)	0.246 (1.3)	0.059 (1.0)	1.77	0.63	0.19	0.16
IL-6	0.470 (1.2)	0.357 (1.2)	0.509 (0.9)	0.05	-0.45	0.82	-0.14
TNF- α	-0.139 (0.5)	-0.130 (0.7)	-0.143 (0.3)	1.72	0.10	0.19	0.02

3.3 Exploratory Factor Analyses

The z-score corrected inflammatory assay data was screened for univariate outliers and no missing data was identified. The KMO index Measure of Sampling Adequacy was greater than 0.50 (KMO= 0.86) and Bartlett's Test of Sphericity was not significant (p= 0.09) indicating that factor analyses would not be suitable to utilize. Further, the inflammatory analytes did not meet the correlation factorability criteria, with correlations less than 0.3, suggesting factorability was not reasonable. As a result, highly correlated networks of inflammatory analytes were not identifiable in this dataset. The minimum amount of data for factor analyses was not satisfied, with a final sample size of 101 and 117 unique inflammatory analytes, there was less than 1 case per variable. Therefore, due to both low sample size and low levels of correlation between inflammatory variables EFA was not feasible for this sample. Subsequent analyses were

completed using the NAPLS2 15-analyte z-score index (Perkins et al., 2015) as well as the individual analytes previously identified to be meaningfully associated with childhood trauma and psychosis symptom severity in existing research.

3.4 Associations between Childhood Trauma, Psychosis Risk Symptoms, Functioning, and Inflammatory Analytes

Partial Pearson Product correlations revealed significant associations between childhood trauma, psychosis risk symptoms, and functioning in CHR subjects, controlling for current tobacco and cannabis use, as well as current antipsychotic and antidepressant medication.

Trauma and Clinical Variables. There was a small, positive partial correlation between total childhood trauma and SOPS positive symptoms ($r(67)= 0.25$, $p= 0.05$), indicating that higher levels of total childhood trauma were associated with greater severity of positive psychosis risk symptoms (**Figure 2**). Further, there was a small negative partial correlation between total childhood trauma and GAF score ($r(67)= -0.27$, $p= 0.03$), indicating that higher levels of total childhood trauma are associated with lower global functioning (**Figure 3**).

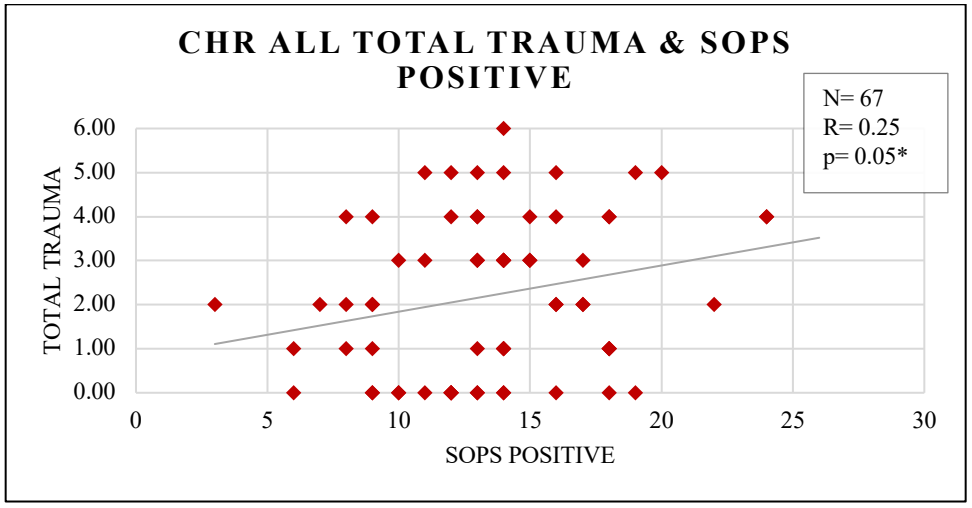


Figure 2. Partial correlation between total incidence of unique trauma and positive psychosis risk symptoms in CHR subjects.

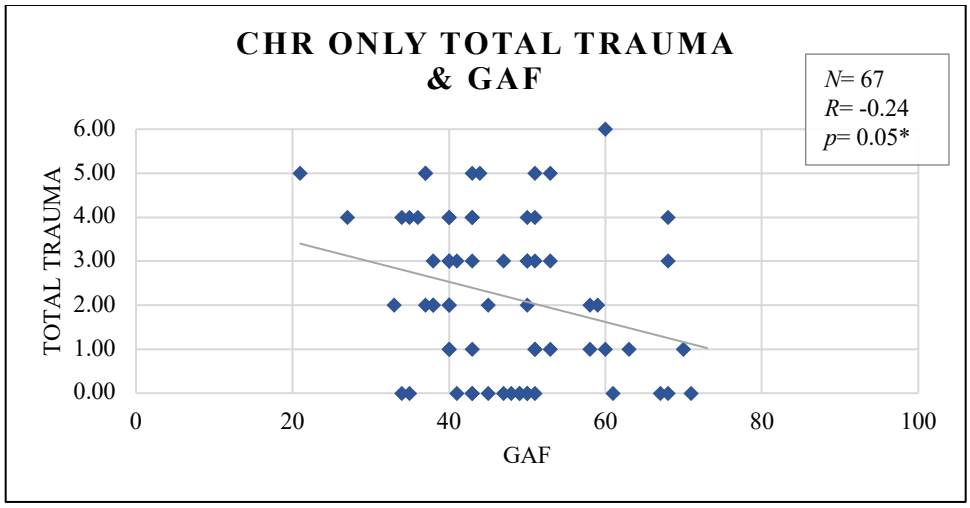


Figure 3. Partial correlation between total incidence of unique trauma and global assessment of functioning and positive psychosis risk symptoms in CHR subjects.

Inflammation and Clinical Variables. There was a small, positive partial correlations between the 15-Analyte Index and SOPS total ($r(67)= 0.36$, $p= 0.004$), SOPS positive ($r(67)= 0.3$, $p= 0.02$), SOPS negative ($r(67)= 0.29$, $p= 0.02$), SOPS disorganized ($r(67)= 0.27$, $p= 0.03$), and SOPS general ($r(67)= .26$, $p= 0.04$) symptoms, indicating that higher levels of the 15-Analyte Index are associated with greater psychosis symptom severity. Further, there were small, negative partial correlations revealed between the 15-Analyte Index and GAF ($r(67)= -0.40$, $p< 0.001$), GFR ($r(67)= -0.27$, $p= 0.04$), GFS ($r(67)= -0.40$, $p= 0.003$), indicating that higher total childhood trauma is associated lower global, social, and role functioning. Finally, there was a small, negative partial correlation between CRP and GFR ($r(67)= -0.29$, $p= 0.02$), indicating that that higher level of CRP is associated with lower role functioning. Cortisol and IL-6 were not significantly associated with total trauma, psychosis risk symptoms, or functioning.

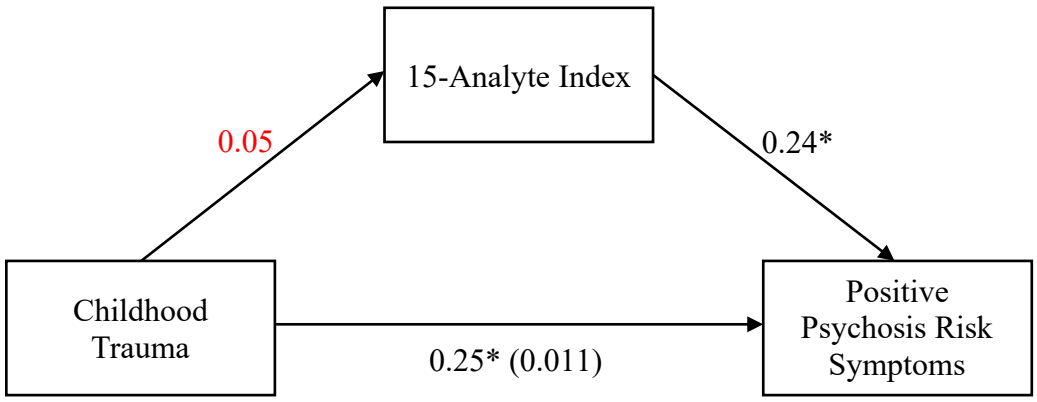
Trauma and Inflammation. Total childhood trauma was not observed to be significantly correlated with the 15-Analyte Index, Cortisol, CRP, TNF-α, or IL-6.

3.5 Multiple Mediation Modeling

Two mediation models were evaluated using the Baron and Kenny (1986) 3-step mediation analysis procedure. Demographic variables that differed between subjects, including, current tobacco and cannabis use, as well as current antipsychotic and antidepressant medication, were added as covariates to the model.

In model 1, regression analyses were used to investigate the hypothesis that inflammation (the 15-Analyte Index) mediates the relationship between total childhood trauma and positive psychosis risk symptoms in CHR subjects. **Figure 4** illustrates, the standardized regression coefficients between the dependent variable (X= childhood trauma), independent variable (Y= SOPS Positive symptoms), and the mediator (M= 15-Analyte Index). First, the regression of total childhood trauma on SOPS positive symptoms, ignoring the mediator, was revealed to be significant (B= 0.57, SE= 0.80, 95% CI[0.01,1.13], β=0.25, t(65)=2.04, p=0.05; R^2= 0.06), indicating that childhood trauma is a significant predictor of SOPS positive symptoms. However, consistent with findings from the correlation analyses, the regression of total childhood trauma on the mediator (15-Analyte Index) was not significant (B= 0.12, SE= 0.33, 95% CI[-0.54, 0.79], β=0.05, t(65)= 0.37, p=0.71; R^2=0.002) indicating that trauma is not a significant predictor of the 15-Analyte Index. Thus, results do not support the mediational hypothesis. However, the regression of inflammation on SOPS, controlling for trauma, step 3 of the analyses, was completed to demonstrate the relationship between variables for future studies. Inflammation was found to be a significant predictor of SOPS positive symptoms (B= 0.22, SE= 0.10, 95% CI[0.01,0.42], β=0.25, t(65)=2.12, p=0.04, R^2=0.067). Finally, when controlling for the mediator (15-Analyte Index), trauma was still a significant predictor of SOPS positive symptoms (B= 0.55, SE= 0.27, 95% CI[-0.01,1.09], β=0.24, t(65)=1.99, p=0.05, R^2=0.122).

These results indicated that indirect effect was not significant, B=0.01, SE= 0.08, 95% CI[-0.08,0.25], completely standardized β=0.01.



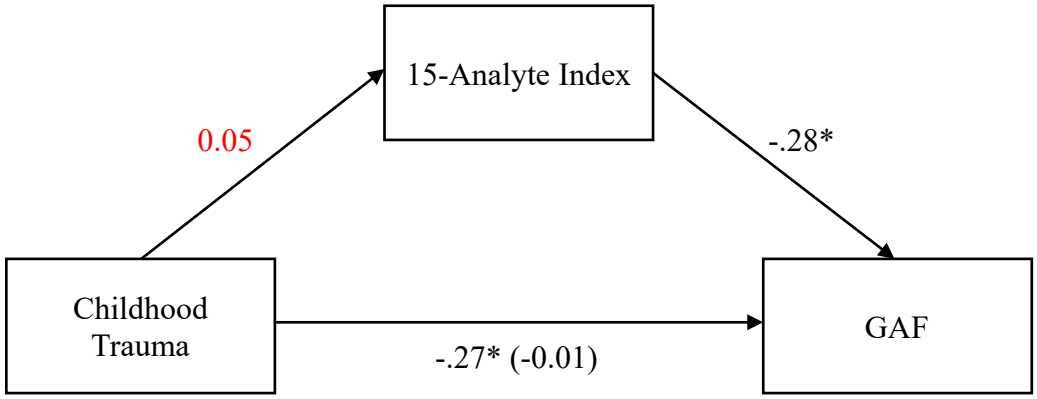
*p <0.05; not significant

Figure 4. *Mediation Model 1*. Standardized Regression Coefficients for the Relationship between Total Childhood Trauma and SOPS Positive Symptom Severity as Mediated by Perkins et al., (2015) 15-Analyte z-score Index.

In Model 2, we evaluated the hypothesis that inflammation (the 15-Analyte Index) mediates the relationship between total childhood trauma and GAF in CHR subjects. **Figure 5** illustrates, the standardized regression coefficients between the dependent variable (X= childhood trauma), independent variable (Y= GAF), and the mediator (M= 15-Analyte Index). First, the regression of total childhood trauma on GAF, ignoring the mediator, was revealed to be significant (B= -1.62, SE= 0.71, 95% CI[-3.07, -0.2], β=-0.27, t(65)=-2.28, p=0.03, R^2=0.074), indicating that childhood trauma is a significant predictor of GAF.

However, consistent with findings from the correlation analyses and Model 1, the regression of total childhood trauma on the mediator (15-Analyte Index) was not significant (B= 0.12, SE= 0.33, 95% CI[-0.54, 0.79], β=0.05, t(65)= 0.37, p=0.71, R^2=0.002) indicating that trauma is not a significant predictor of the 15-Analyte Index. Thus, results do not support the mediational hypothesis. However, the regression of inflammation on GAF, controlling for

trauma, step 3 of the analyses, was completed to demonstrate the relationship between variables for future studies. The 15-Analyte Index was found to be a significant predictor of GAF (B= -0.62, SE= 0.25, 95% CI[-1.12, -0.11], β=-0.28, t(65)=-2.42, p=0.02, R^2=0.084). Finally, when controlling for the mediator (15-Analyte Index), trauma was still a significant predictor of GAF (B= -1.5, SE= 0.69, 95% CI[-2.92, -0.17], β= -0.26, t(65)= -2.25, p=0.03, R^2=0.151). These results indicated that indirect effect was not significant, B=-0.07, SE= 0.24, 95% CI[-0.69, 0.30], completely standardized β=-0.01.



*p <0.05; Not significant

Figure 5. *Mediation Model 2.* Standardized Regression Coefficients for the Relationship between Total Childhood Trauma and Global Assessment of Functioning as Mediated by Perkins et al., (2015) 15-Analyte Index.

3.6 Exploratory Analyses

Exploratory MANCOVA using Bonferroni post-hoc were used to compare between subjects' effect of psychosis conversion status and trauma history in CHR subjects on clinical, functional, and inflammatory analytes demonstrated to differ between UC and CHR subjects in Hypotheses 1a, 1b, and 1c. The 67 CHR subjects were stratified by conversion status and history of trauma to yield 4 groups: 1. no known progression to psychosis and absence of trauma history (CHR-$NC_{NoTrauma}$; n=8), 2. known progression to psychosis and absence of trauma history (CHR-

$C_{NoTrauma}$; n= 9), 3. no known progression to psychosis and history of trauma (CHR-NC_{Trauma}; n= 30), and 4. known progression to psychosis and conversion to psychosis and history of trauma (CHR-C_{Trauma}; n=20). There was a significant effect of conversion status and history of trauma on the combined dependent variables after controlling for current tobacco and cannabis use, as well as current antidepressant and antipsychotic medications [$F(42, 131.3)=1.99$, $p= 0.002$, Wilk's $\Lambda=0.232$, $\eta^2 = 0.385$)]. Univariate tests revealed significant between group differences for SOPS Positive symptom severity [$F(3, 57)=4.63$, $p= 0.006$, $\eta^2 = 0.196$)], GAF [$F(3, 57)= 313.43$, $p= 0.03$, $\eta^2 = 0.143$)], and the 15-Analyte Index [$F(3, 57)$, 14.7 $p< 0.001$, $\eta^2 = 0.436$)]. Between group differences were not observed in CRP, TNF-α, SOPS negative, SOPS disorganized, SOPS general, SOPS total, GFR, or GFS. As seen in **Figure 6**, Post-Hoc comparisons, using the Bonferroni procedure, revealed that CHR-C_{Trauma} subjects exhibited significantly higher SOPS positive symptom scores (M= 16.0, SD= 3.7) as compared to CHR-$C_{NoTrauma}$ (M= 11.3,SD= 1.7, p=0.021), CHR-NC_{Trauma} (M= 12.6, SD= 4.4, p=0.01, *d*= 0.84), and CHR-$NC_{NoTrauma}$ subjects (M= 13.04, SD= 4.5, p= 0.05). Further, CHR-C_{Trauma} subjects demonstrated significantly lower GAF scores (M= 40.8, SD= 8.1) as compared to CHR-$NC_{NoTrauma}$ subjects (M= 50.3, SD= 10.3, p=0.04), but not CHR-$C_{NoTrauma}$ (M= 47.7, SD= 9.7) or CHR-NC_{Trauma} subjects (M= 49.3, SD= 10.6). Finally, CHR-C_{Trauma} and CHR-$C_{NoTrauma}$ demonstrated significantly higher scores on the 15-Analyte Index (CHR-C_{Trauma}: M= 7.68, SD= 2.9; CHR-$C_{NoTrauma}$: M= 7.68, SD= 2.87) compared to CHR-$NC_{NoTrauma}$ subjects (M= 0.75, SD= 4.7 p=0.01) and CHR-NC_{Trauma} subjects (M= 1.54, SD= 3.8, p=0.01), but did not significantly differ from one another (p=1.0).

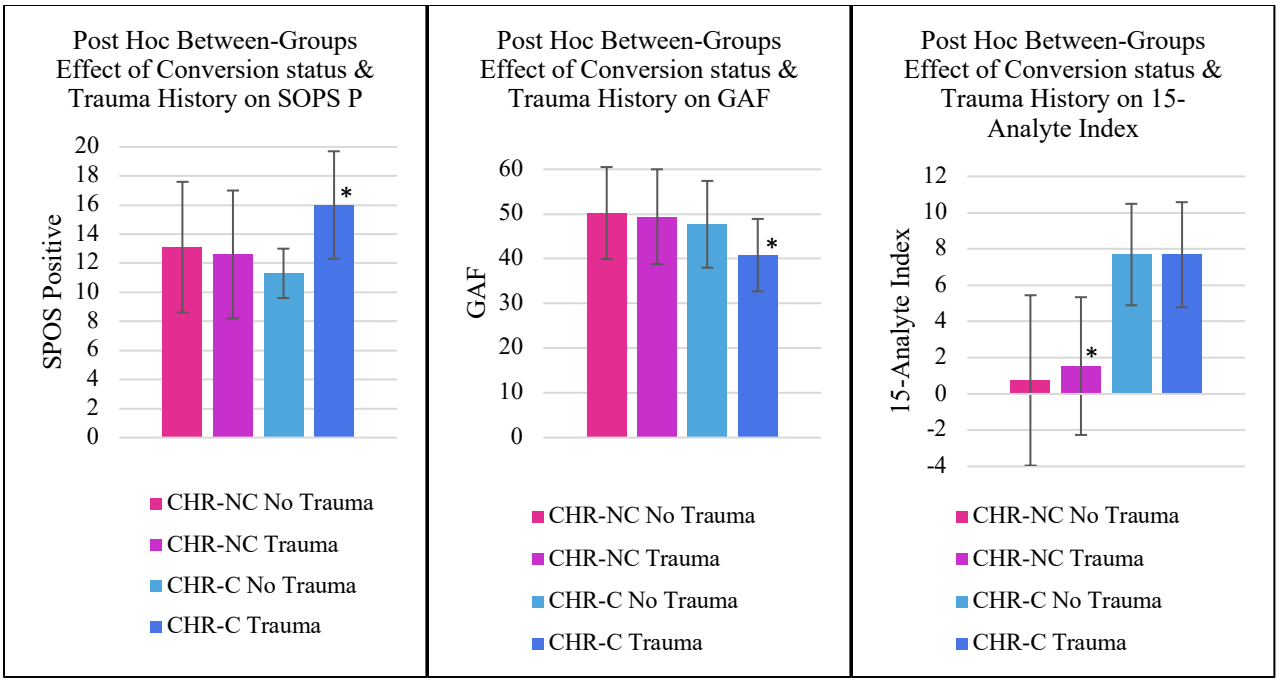


Figure 6. MANCOVA Bonferroni Post-Hoc comparisons evaluating effect of conversion status and history of trauma on between group differences in SOPS Positive, GAF, and the 15-Analyte Index (N=67)

4. Discussion

This study sought to examine the associations between childhood trauma, psychosis risk symptoms, functioning, and inflammatory analytes in a sample of 67 CHR subjects (29 of which are known to have progressed to psychosis) and 34 UCs, thus contributing to a growing body of literature examining the effect of early life adversity on later life outcomes in individuals at risk for psychosis and identifying associated biological mechanisms. More specifically, this study sought to examine whether inflammation mediates the relationship between childhood trauma and clinical outcomes (including psychosis risk symptoms and functioning) in individuals at risk for psychosis. This is one of few studies to explore whether inflammatory analytes mediate the relationship between childhood trauma and psychosis risk symptoms or functioning in CHR subjects, providing important implications for clinical intervention in youth at risk for psychosis

by helping to uncover biological mechanisms for therapeutic intervention. However, this is the first study to evaluate this hypothesis using an enhanced sample of CHR subjects.

4.1 Group Differences in Childhood Trauma, Psychosis Risk Symptoms, Functioning, and Inflammatory Analytes

The first primary aim of this study was to confirm known group differences between CHR and UC subjects in experience of childhood trauma, psychosis risk symptoms, and functioning, as well as evaluate groups differences across inflammatory analytes known to be associated with childhood trauma. First, we hypothesized that CHR subjects would demonstrate higher levels of proinflammatory markers known to be associated with experience of childhood trauma (Cortisol, CRP, IL-6, and TNF-α) as well as the 15-Analyte Index developed by Perkins et al. (2015) relative to UC subjects. Interestingly, CHR individuals in this sample demonstrated lower levels of TNF-α as compared to UCs, which is inconsistent with research demonstrating significantly elevated baseline blood plasma levels of TNF-α, CRP, and IL-6 in CHR individuals who endorsed a history of trauma (Baumeister et al., 2016). Significant differences were not revealed for Cortisol, CRP, IL-6 or the 15-Analyte Index between UC and CHR groups. The non-significant findings of differences in the 15-Analyte Index is attributable to the index being derived to discriminate between subjects who progress to psychosis, versus those that do not, and unaffected individuals, thus grouping the CHR subjects together resulted in non-significant differences between CHR and UC groups.

Further, TNF-α is a proinflammatory cytokine, and thus, is involved in the initiation and aggravation of inflammatory responses, including cell apotosis. Interestingly, the biology of TNF in the brain allows for it to both protect neurons, as well as initiate their destruction through different protein activation processes (Dinarello, 2000). Although we are unable to evaluate this

type of process in the current dataset, the observed decreased levels of TNF-α between CHR and UC subjects may relate to a meaningful narrative of complex inflammatory activation and suppression processes associated with enduring effects of childhood trauma such as increased stress reactivity in individuals at risk for psychosis (Agnew-Blais & Danese, 2016; Danese & Baldwin, 2017; Danese et al., 2009). For example, Jeffries et al. (2018) reports that as compared to CHR-NC, CHR subjects who convert to psychosis demonstrate a striking loss of complexity in analyte correlation networks that could be prognostic, indicating that network imbalance in pro-inflammatory suppression and activation processes is an important feature of in understanding progression to psychosis.

Second, we hypothesized that CHR subjects would demonstrate significantly higher incidence of childhood trauma, greater severity of psychosis risk symptoms, as well as lower global, social, and role functioning as compared to UC subjects. Consistent with our hypothesis, this subsample of CHR participants demonstrated significantly higher overall psychosis risk symptoms severity, as measured by the SOPS, and lower functioning on the GAF, GFS, and GFR as compared to UC subjects. By definition, CHR individuals experience more psychosis risk symptoms and lower functioning as compared to unaffected individuals (T. J. Miller et al., 2003). Thus, the findings that CHR subjects in this sample demonstrated higher psychosis-risk symptoms and lower functioning is to be expected. More importantly, as compared to UC, CHR subjects in this sample demonstrated significantly higher total unique trauma, as well as higher incidence of trauma on most individual trauma subtypes, including, psychological bullying, physical bullying, emotional neglect, psychological abuse, and physical abuse. Three-fourths (74.6%) of CHR subjects in this sample reported history of childhood trauma, which is consistent with previous reports that prevalence of childhood trauma in individuals at risk for psychosis

may be up to 90% (Kraan et al., 2015); however, this proportion is higher than larger sample from which this data was derived (N=540; CHR n= 360 and UC n= 180) with approximately 60% of all CHR subjects reporting history of trauma. Thus, results from this study replicate previously demonstrated findings from Addington et al. (2013), that CHR subjects experienced greater total number of unique trauma and bullying than UC subjects; however, this subsample of participants also demonstrates significant differences in emotional neglect, psychological abuse, and physical abuse, which was not demonstrated in the larger sample. Although only CHR subjects demonstrated a history of sexual abuse, the group differences between CHR and UC subjects was not significant. We can hypothesize that since the current sample of CHR subjects is enriched with a higher proportion of individuals who are known to have converted to psychosis (thus demonstrating higher psychosis risk symptom severity and poorer functioning at baseline), that increased childhood trauma is associated with poorer clinical outcomes in this CHR sample, which was further explored in Aim 4.

Finally, we hypothesized that CHR subjects who experienced history of childhood trauma (CHR_{Trauma}) would demonstrate higher levels of proinflammatory markers known to be associated with experience of childhood trauma (Cortisol, CRP, IL-6, and TNF-α) as well as the 15-Analyte Index developed by Perkins et al (2015), higher levels of baseline psychosis symptom severity, and lower baseline global/social/role functioning relative to CHR subjects with no history of childhood trauma ($CHR_{NoTrauma}$) and that these differences would vary by trauma subtype. Inconsistent with our hypothesis, no differences were observed between CHR_{Trauma} and $CHR_{NoTrauma}$ subjects in levels of the 15-Analyte Index, Cortisol, CRP, TNF-α, or IL-6. However, when analyzing groups by subtype of trauma, it was revealed that CHR individuals who endorsed psychological bullying, physical abuse, and sexual trauma also

demonstrated higher total incidence of trauma as compared to CHR subjects that did not endorse one of those subtypes of trauma. Further, CHR_{Trauma} subjects who endorsed a history of psychological bullying demonstrated significantly lower Cortisol than CHR_{Trauma} individuals with no history of psychological bullying. While blunted morning salivary Cortisol response in has been observed in first episode psychosis subjects who experienced a higher incidence of childhood trauma (Mondelli et al., 2010), the opposite effect has been seen with blood based Cortisol. In this sample, higher levels of blood based markers of Cortisol were associated with conversion to psychosis in this sample and added as one of the 15-analytes in the Perkins et al. (2015) index. Further, (Addington et al., 2013) reported that higher incidence of psychological bullying was associated with poorer global role functioning in CHR subjects. Thus, while we know increased levels of Cortisol are important to predicting conversion to psychosis and it is possible that the lower levels of Cortisol seen here as associated with higher levels of childhood trauma is associated with a different phenomenon (i.e. childhood trauma is differentially important to predicting poorer outcomes such as lower functioning in individuals at risk for psychosis, but not conversion to psychosis). Put more simply, these results may indicate that the association or difference between blood-based Cortisol and childhood trauma is not clinically relevant for conversion to psychosis and that childhood trauma is independently predictive of clinical or functional outcomes, while higher levels of blood based Cortisol are predictive of conversion status.

4.2 Factorability of Inflammatory Analytes using EFA

The second primary aim of this study was to identify highly correlated networks of inflammatory analytes using exploratory factory analysis. However, lack of correlation between inflammatory analytes and the relatively small sample size indicated that the sample was not

suitable for factor analysis. To our knowledge, only one study to date has used EFA to understand the correlation between inflammatory cytokines and severity of psychosis symptoms (Dimitrov et al., 2013), demonstrating positive correlations between levels of cytokines and the Positive and Negative Symptoms Scale (PANSS) scores in subjects with schizophrenia. (Jeffries et al., 2018) used unweighted co-expression network analyses to identify highly correlated networks of analytes in CHR and HC subjects, providing evidence of marked simplification of networks of correlated proteins that regulate tissue remodeling consistent with a hypothesis of blood-brain-barrier dysregulation in schizophrenia. Thus, the investigation of both clusters of inflammatory analytes and networks of inflammatory analytes is important to improving our understanding of high complex interplay between pro-inflammatory and anti-inflammatory processes in the development of psychosis and clinical outcomes.

4.3 Associations between Childhood Trauma, Psychosis Risk Symptoms, Functioning, and Inflammatory Analytes

The third primary aim of this study was to determine the relationship between childhood trauma, psychosis risk symptom severity, and functioning in CHR. First, we hypothesized that there would be a significant positive relationship between childhood trauma, and psychosis risk symptom severity, as well as a significant negative relationship between childhood trauma and global/social/role functioning. Consistent with our hypothesis, partial correlation analyses revealed that total childhood trauma was associated with greater positive psychosis risk symptoms (SOPS Positive) and lower global functioning (GAF). Both findings are novel compared to Addington et al. (2013); however, we were unable to replicate the finding that total childhood trauma is associated with global role functioning in this smaller subsample. The association between childhood trauma and positive psychosis risk symptoms is consistent with

existing research that higher incidence of trauma is associated with higher levels of positive symptoms in CHR (Kraan et al., 2015; Loewy et al., 2019; Thompson et al., 2009). An extensive review on the relationship between childhood trauma and schizophrenia (Read et al., 2005), concluded that childhood trauma is strongly related to symptoms of psychosis, specifically hallucinations and that the relationship may be dose-dependent.

Second, we hypothesized that there would be a significant positive relationship between inflammation, total childhood trauma, psychosis risk symptom severity, and functioning, as well as a significant negative relationship between global/social/role functioning and inflammatory analytes in CHR subjects. Consistent with our hypothesis and replicating results from Perkins et al. (2015), the 15-Analyte Index was positively correlated with all SOPS domains and negatively correlated with social, role, and global functioning in CHR subjects. However, a novel finding in this sample was revealed, a negative correlation between CRP and role functioning, indicating that higher levels of CRP are associated with lower scores on GFR. As GFR measures the level of impairment in academic, occupational, and homemaking roles, this is consistent with research linking blood levels of CRP to impaired cognitive performance in acute psychosis (Johnsen et al., 2016). Further, (Jacomb et al., 2018) demonstrated that higher levels of CRP were associated with significantly worse working memory and inversely correlated with cortical thickness in individuals diagnosed with schizophrenia. Thus, the association between higher CRP and lower GFR may be a marker of impaired cognitive performance in CHR subjects.

Inconsistent with our hypothesis, inflammatory analytes were not associated with total childhood trauma in CHR subjects. Previous research demonstrating the association between inflammation and childhood trauma and psychosis used a measure of childhood trauma that captured severity and chronicity of trauma occurrence. For example, (Dennison et al., 2012)

demonstrated associations between TNF-a and severity of childhood trauma in first episode subjects using the CTQ which captures not only presence of trauma, but also severity and of the trauma experienced (Bernstein et al., 1997). Further, Hepgul et al. (2012) demonstrated associations between childhood trauma and CRP using The childhood experience of care and abuse scale: CECA.Q (Bifulco, Bernazzani, Moran, & Jacobs, 2005), which also measures severity of trauma. Thus, the measurement of childhood trauma used in this study did not capture severity or chronicity of the trauma experienced and thus were unable to be examined in the current study.

Finally, we hypothesized that inflammation would partially mediate the relationship between childhood trauma and psychosis-risk symptom severity, as well as between childhood trauma and functioning in CHR youth. Using the information gathered from partial correlation analyses, we tested two mediation models. In Model 1, we explored whether the relationship between total childhood trauma and SOPSP was mediated by the 15-Analyte Index. In Model 2, we explored whether the relationship between total childhood trauma and GAF was mediated by the 15-Analyte Index. Inconsistent with our hypothesis, but consistent with the results from the partial correlation analyses, total childhood trauma and the 15-analyte index independently accounted for a significant proportion of variance in SOPS positive symptoms in Model 1. Further, total childhood trauma and the 15-analyte index independently accounted for a significant proportion of variance in GAF in Model 2. Neither model showed significant mediating effect of inflammation on the relationship between childhood trauma and clinical outcome due to lack of association between inflammation and childhood trauma. Thus, we can conclude that childhood trauma and the 15-Analyte Index may have additive effects in predicting

SOPS positive and GAF, and that the effects of total childhood trauma on clinical outcomes is not mediated by inflammatory processes.

These results have several possible explanations. It is possible that the lack of association between childhood trauma and inflammation was due to the inability to account for severity of childhood trauma experienced. Thus, with a measure of severity of childhood trauma, perhaps the relationship between total severity/chronicity of trauma experienced would be associated with Cortisol, CRP, IL-6, TNF-a, or the 15-Analyte index. However, it is also possible that the individual analytes included in the 15-analyte index are uniquely and independently predictive of SOPS positive symptoms and GAF, thus childhood trauma may not be associated with those specific inflammatory analytes irrespective of the childhood trauma indices used. Several studies cite the significant relationships between inflammation, childhood trauma, and in first episode psychosis (Misiak et al., 2017), (Aas et al., 2014; Barker, Gumley, Schwannauer, & Lawrie, 2015), but no studies to our knowledge to date have evaluated the mediating effect of inflammation on the relationship between childhood trauma and clinical outcomes in CHR subjects to date.

4.4 Exploratory Analysis of group differences across conversion status and history of childhood trauma

Lastly, we explored the effect of psychosis-risk conversion status and trauma history on inflammation, psychosis risk symptom severity, and functioning in CHR. Group stratification revealed that there were no significant differences between CHR-C and CHR-NC groups in total trauma, meaning that CHR individuals who progressed to psychosis from an at-risk state did not demonstrate higher total trauma as compared to CHR subjects that did not progress to psychosis. MANCOVA revealed significant between groups differences in SOPS P, GAF, and the 15-

Analyte Index. Post-Hoc analyses using Bonferroni correction revealed that CHR- C_{Trauma} subjects with a history of childhood trauma demonstrated significantly higher SOPS positive symptom scores than CHR- $C_{NoTrauma}$, and CHR- NC_{Trauma}, CHR- $NC_{NoTrauma}$ subjects. Given that criteria for conversion to psychosis is based on increased scores in the SOPS Positive scale, total childhood trauma may be an important independent variable associated with increased baseline SOPS positive symptoms and help identify a category of individual who are highest risk for conversion to psychosis. Further, CHR-C_{Trauma} demonstrated lower GAF as compared to CHR-$NC_{NoTrauma}$ subjects, whereas CHR- $C_{NoTrauma}$ did not demonstrate differences in GAF scores compared to either group of CHR-NC subjects. This again may imply that history of childhood trauma may be an important independent variable associated with increased baseline global functioning and thus help identify a category of clinical high-risk subjects who demonstrate the lowest global functioning. Finally, the 15-Analyte index did not differ between CHR-C_{Trauma} and CHR-$C_{NoTrauma}$ subjects but did differ between CHR-NC_{Trauma} and CHR-$NC_{NoTrauma}$ groups. Given that higher scores on the 15-Analyte index are associated with higher SOPS overall symptoms, lower global functioning, and lower social/role functioning, this finding may be interpreted to mean that CHR subjects with any history of trauma may demonstrate a unique population of subjects with worse clinical outcomes who would benefit most from early intervention.

4.5 Limitations and Future Directions

There are several possible limitations of this study that may explain the non-significant association between history of childhood trauma and pro-inflammatory cytokines (CRP, IL-6, and TNF-a). While sample size was adequate to detect small to medium between subjects' effects, due to employing multiple between-subjects comparisons, risk for Type I error was increased. Future research may consider use of open public data sets or consortium efforts in

order to pool resources and maximize recruitment of sufficient samples to conduct analyses that require a large sample of subjects, such as exploratory factor analyses of inflammatory analytes.

Further, measurement of childhood trauma in this study prevents evaluation of the effect of chronicity and severity of trauma to be evaluated. Future studies should consider use of the non-abbreviated Childhood Trauma Questionnaire: CTQ, (Bernstein et al., 1997) in order to capture severity and chronicity of each individual subtype of trauma endorsed. A review by Schafer and Fisher (2011a) determined that instruments assessing childhood trauma, such as the CTQ, that were originally developed for the general population are also appropriate for use among people with psychosis. However, the use of self-report measures of childhood trauma is additionally prone to bias, particularly when subjects are under the age of 18. Thus, in order to prevent bias in reporting, future studies should employ use of informants that may be able to verify experience of childhood trauma (such as caretakers) in order to increase reliability of reporting.

Moreover, inflammatory analytes and childhood trauma were only evaluated from one time point. Due to the age range of the at-risk sample (12-30), this might mean that ongoing changes in inflammatory analytes and additional trauma experiences that occurred during the course of the study, were not captured. Ongoing sampling of childhood trauma on inflammation must be evaluated across time in order to establish more reliable measures of these dynamic processes. The use of cross-sectional data for mediation analyses is limited, as temporal precedence cannot be established thereby preventing implications to be drawn regarding the causal effect of childhood trauma or inflammatory markers on clinical outcomes. While a study bySimpson et al. (2019) demonstrated that self-report measurement of childhood trauma in a first episode psychosis sample remained stable and consistent across multiple time points, they found

that severity of trauma reported did fluctuate across multiple assessments. If unable to collect multiple biological samples from different time points, implementation of a stress test design with blood marker sampling would allow for testing the impact of trauma on stress reactivity and inflammatory response during the course of one visit. Additionally, the validation of inflammatory markers in psychosis is ongoing; therefore, selection of specific markers of inflammation to measure at various phases of illness is not well established, nor is there a clear understanding of what inflammatory analytes may be differentially impacted by environmental stress as compared to disease progression. Measuring a large panel of serum markers of inflammation is preferable, but studies must be well-powered in order to establish reliable effects. Evaluating profile networks of inflammatory analytes is needed to understand the dynamic activation and suppression of analytes and provide a clearer understanding of immune system regulation as a whole, as compared to understanding of single analytes. Measurement of single inflammatory analytes provides only a small snapshot of a much larger and more complex picture that is the immune system.

Finally, this study lacked assessment of variables known to affect inflammatory analyte levels, namely body mass index (BMI). While this study controlled for the effects of antipsychotic, antidepressant, tobacco, and cannabis use, BMI is highly associated with inflammation and thus may have confounded findings in inflammatory analytes.

4.6 Summary and Clinical Implications

Taken together these results confirm existing research that individuals at CHR for psychosis demonstrate higher total childhood trauma as compared to unaffected comparison subjects and that history of childhood trauma is associated with increased positive psychosis-risk symptoms and worse global functioning. However, total childhood trauma was not associated

with inflammation in this sample, thus analyses of the mediating effect of inflammatory analytes in the relationships between childhood trauma and clinical outcomes was non-significant. Instead, this study suggests that total childhood trauma and inflammatory analytes independently predict positive psychosis risk symptoms and lower global functioning; thus, these independent effects are additive. These findings confirm the importance of assessing for childhood trauma and blood-based inflammation in at-risk subjects as a means to identify individuals who may be at the highest risk for poor clinical and functional outcome.

Childhood trauma and inflammation may seem difficult variables to target through existing evidence-based psychotherapy interventions. However, there is a growing body of research that supports the use of complementary and alternative medicine (CAM) psychosocial interventions that may effectively target these factors in psychosis. The goal of research of CAM in psychosis is to replicate results from studies conducted in the general population demonstrating that the use of mind-body interventions reduces reactivity to stress and chronic inflammation. For example, research Breines et al. (2014) demonstrated that higher levels of "self-compassion," defined by Neff (2011) as "the attitude of treating oneself with kindness and non-judgmental understanding," are associated with reduced IL-6 response in reaction to stress. More importantly, it has been demonstrated that self-compassion is not a "trait," but rather a modifiable and alterable "state." Cognitively-Based Compassion Training (CBCT) is a meditation-based program derived from Tibetan Buddhist mind-training that has been demonstrated to enhance empathy and compassion for oneself and others. Research on CBCT in medically stable populations by Pace et al. (2009) reveals 6 weeks of compassion meditation training reduced stress-induced immune responses (IL-6 and Cortisol) in a stress-test design. Further, Pace et al. (2010) demonstrate that strength of reduction in immune response was not

mediated by time spent meditating, indicating that benefits of compassion training are not dependent on long hours of practice. This is very relevant to the application and effectiveness of such techniques in children or adolescents, particularly those currently experiencing mental health concerns, given that it would be impractical to expect children with mental health concerns to engage in lengthy meditation practice. In fact, Pace et al. (2013) demonstrated the feasibility of CBCT in not only adolescents, but those in foster care with a history of early life adversity. Moreover, foster care program adolescents with a history of childhood trauma demonstrated significant reductions in salivary CRP after just 6-weeks of compassion training. Compassion training has not yet been evaluated in CHR population, but there is evidence that adapted mindfulness-based interventions are not only safe and therapeutic for use in chronic psychosis populations, but also may help to decrease individual distress around positive psychosis symptoms, such as auditory hallucinations and delusions (Chadwick, 2014). A recent systematic review by Louise, Fitzpatrick, Strauss, Rossell, and Thomas (2017) on "third-wave" cognitive behavioral interventions in psychosis, reveals that acceptance-based interventions (which include mindfulness techniques) show moderate effects in reducing depressive symptoms, but no effect in reducing distress around psychosis symptoms or improving functional outcome. Randomized-controlled clinical trials utilizing mindfulness-based interventions for early-psychosis are currently lacking. Nonetheless, these techniques represent a promising category of psychosocial intervention warranting further study as they may modify reactivity to stress and immune response.

Other CAM interventions that warrant further study in psychosis populations to target immune response and clinical outcomes include exercise, diet, and cannabidiol. Exercise and diet have been shown to have robust effects on reducing chronic inflammation and improving health

outcomes in the adolescents (Wärnberg et al., 2009; Wärnberg et al., 2007). Research on aerobic exercise in psychosis groups has demonstrated very promising findings, indicating that moderately intense exercises, such as walking or bike riding, may improve positive and negative psychosis risk symptomatology, cognition, and functional outcome (Firth et al., 2017). Further, these effects have been replicated in CHR populations (Mittal et al., 2017). Diet may be another window of opportunity for impacting clinical outcomes and immune response in psychosis. For example, a recently review by Stogios et al. (2020) reveals that unmedicated individuals with psychosis demonstrate increased appetite and cravings for fatty foods, which contribute to weight gain and metabolic disturbances known to be associated with higher levels of inflammation. Wu, Wang, Bai, Huang, and Lee (2007) revealed that a 6-month combined diet and physical activity program in schizophrenia subjects resulted in reduced BMI, improved metabolic profiles of insulin and triglycerides, as well as improved psychotic symptoms. Cahn, Goodman, Peterson, Maturi, and Mills (2017) demonstrated a 3- month mindfulness, diet, and yoga combined intervention resulted in increased levels of BDNF and increased cortisol awakening response in a population of medically stable adults. Research on novel therapeutics, such as cannabidiol (CBD), as a potential treatment for psychosis have demonstrated that CBD may not only have neuroprotective, antioxidant, and anti-inflammatory effects, but also improve disease trajectory of psychosis by reducing positive psychosis symptoms, anxiety, and cognitive deficits in first episode psychosis groups (Hahn, 2018). To date, there are no studies evaluating the effects of diet, exercise, CBD, or combined interventions on immune response to stress in CHR psychosis populations; however, there is strong evidence to warrant further study of these interventions in CHR psychosis groups.

Finally, therapeutic interventions that are known to improve clinical outcomes for individuals who have experienced childhood trauma may be particularly important in mitigating long term functional impairments in youth at clinical high risk for psychosis. Bendall, Alvarez-Jimenez, Nelson, and McGorry (2013) describe several recommendations to be considered for good, quality, assessment and intervention withing individuals at risk for psychosis endorsing a history of childhood trauma, including, systematic inquiry about childhood trauma for all individuals with psychosis, and development of individualized treatment plan adapted from cognitive behavioral therapy approaches for the treatment of psychosis and trauma, paying particular attention to pacing of treatment and repeated assessment. Evidence based psychotherapies for trauma that include focus on stress management and interpersonal effectiveness such as Skills Training in Affect and Interpersonal Regulation (STAIR), may be particularly meaningful for CHR subjects who have a history of childhood trauma. Schafer and Fisher (2011b) demonstrated the effectiveness and tolerability of STAIR for individuals at clinical high risk for psychosis with history of childhood trauma. However, there has been little research evaluating the effectiveness of evidence-based trauma-focused treatments in this complex population. Studies evaluating the effectiveness of trauma focused interventions may include individuals with psychosis as only a small sub-sample of participants included in the research, but co-occurring psychosis spectrum disorders are often included as exclusionary criteria in evaluation of trauma-focused treatments for individuals with a history of trauma (Bendall et al., 2013). As previously discussed, compassion training, such as CBCT, may represent a unique category of psychosocial intervention that helps to improve stress reactivity in youth who have experienced early life adversity (Pace et al., 2013). Moreover, Poehlmann-Tynan et al. (2020) demonstrated when parents completed 8-10 weeks of CBCT their children

(infants and toddlers) demonstrated reduced cortisol, indicating that compassion training for parents may have cascading effects of cumulative stress on their children. Although difficult to achieve, prevention of the occurrence of childhood trauma would be an ultimate goal. Varese et al. (2012) maintain that if childhood trauma was removed from the population entirely, the number of individuals presenting with psychosis would be reduced by 33%. Thus, assessment of childhood trauma is an essential first step toward not only early intervention in, but also ultimately prevention of psychosis spectrum disorders.

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