The association between premorbid adjustment and childhood trauma in first-episode schizophrenia spectrum disorders

by

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DECLARATION

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ABSTRACT

Introduction: Childhood trauma is a worldwide phenomenon that refers to a broad range of adverse experiences occurring during childhood and adolescence, including emotional, sexual and physical abuse, as well as physical and emotional neglect. Childhood trauma is a risk factor for schizophrenia. However, the mechanisms whereby childhood trauma contributes to the risk for schizophrenia remain unclear. One possible mechanism could be that a history of childhood trauma contributes to poorer premorbid adjustment as an indicator of neurodevelopmental compromise and a proxy for those who go on to develop schizophrenia. The objectives of the present study were to examine the associations of childhood trauma type and timing with premorbid functioning in first-episode schizophrenia spectrum disorders (FES).

Methods: The present cross-sectional study included 111 individuals with FES. Patients were assessed using the Childhood Trauma Questionnaire, short form (CTQ-SF), the Life Events Checklist (LEC-5), the Premorbid Adjustment Scale (PAS), and the Life Events Timeline. Pearson correlations were calculated to determine the linear associations of different childhood trauma subtypes with specific domains of premorbid adjustment. The initial analyses were used to inform subsequent hierarchical regressions modelling for the effects of childhood trauma on premorbid functioning.

Results: Total childhood trauma scores did not demonstrate a significant relationship with overall premorbid adjustment. However, physical neglect showed a significant relationship with poorer premorbid social adjustment in early adolescence. Furthermore, timing of childhood trauma did not moderate the relationship between childhood trauma and premorbid adjustment.

Conclusion: Physical neglect could increase the risk for schizophrenia through mechanisms that negatively affect premorbid adjustment. The study highlights the impact of socio-economic circumstances on mental health. This is an important topic for mental health professionals working in South Africa, a country with high levels of poverty. However, the study was cross-sectional in nature, and therefore causality could not be inferred. It would be important to replicate the study findings in a larger representative sample and to conduct a longitudinal study to determine if childhood physical neglect has long-lasting effects on patient outcomes.

Keywords: schizophrenia spectrum disorders, childhood trauma, premorbid adjustment, physical neglect, timing of childhood trauma

OPSOMMING

Inleiding: Trauma tydens kinderjare kom wêreldwyd voor. Trauma tydens kinderjare verwys na ‘n breë spektrum van ongewenste ervaringe wat gedurende kinderjare en adolossensie plaasvind en sluit in emosionele, seksuele en fisiese mishandeling, asook fisiese en emosionele verwaarlosing. Individue wat gedurende hulle kinderjare trauma ervaar het, het ‘n groter kans om skisofrenie te ontwikkel as diegene wat geen trauma ervaar het nie. Nie te min, presies hoe hierdie trauma bydra tot die ontwikkelling van skisofrenie is steeds onduidelik. Een moontlike meganisme is dat ‘n geskiedenis van kinderjare trauma bydra tot swakker premorbiede aanpassing. Premorbiede aanpassing is ‘n indikasie van neuro-ontwikkelings agterstande en ‘n voorloper vir diegene wat dan later skisofrenie ontwikkel. Die doel van die huidige studie was om die assosiasies van kinderjare trauma, tipe en tydperk met premorbiede aannpassing te bestudeer, in ‘n steekproef van eerste-episode skisofrenie spektrum versteurings (EEV).

Metode: Die studie het gebruik gemaak van ‘n kruis-deursnit ontwerp en het 111 individue met EEV ingesluit. Die pasiënte was ge-evalueer met die verkorte weergawe van die Kinderjare Trauma Vraelys (CTQ-SF), die Lewens Gebeurtenisse Kontrole Lys (LEC-5), die Premorbiede Aanpassings Skaal (PAS) en die Lewens Ervaringe Tydlyn. Pearson korrelasies was gedoen om potensieële korrelasies tussen kinderjare trauma veranderlikes en premorbiede aanpassing te identifiseer. Die inisieële analiese was gedoen om ‘n daarop volgende hiërargiese regressie model te lei, in die ondersoek na die effek van kinderjare trauma op premorbiede funksionering.

Resultate: Die totale kinderjare trauma telling het nie ‘n beduidende verwantskap met globale premorbiede aanpassing getoon nie. ‘n Beduidende verwantskap tussen fisiese verwaarlosing en swakker sosiale premorbiede aanpassing gedurende vroeë adolossensie was wel bevind. Verder was die tydperk van kinderjare trauma nie ‘n moderator van die verhouding tussen kinderjare trauma en premorbiede aanpassing nie.

Gevolgtrekkings: Fisiese verwaarlosing kan die risiko om skisofrenie te ontwikkel verhoog deur meganismes wat premorbiede aanpassing negatief beïnvloed. Die studie beklemtoon die impak van sosio-ekonomiese omstandighede op geestesgesondheid. Dit is ‘n belangrike faktor wat professionele geestesgesondheidsorg praktisyns werksaam in

Suid Afrika in ag moet neem, siende dat die land ‘n hoë voorkoms van armoede het. Die kruis-deursnit aard van die studie laat dit egter nie toe om gevolgtrekkings te maak oor of skisofrenie dirêk veroorsaak word deur kinderjare trauma nie. Dit is belangrik om die studie bevindinge te repliseer in ‘n groter verteenwoordigende steekproef, asook om ‘n longitudinale studie te doen om vas te stel of fisiese verwaarlosing gedurende kinderjare ‘n langdurige effek het op pasiënt uitkomste.

Sleutelwoorde: skisofrenie spektrum versteurings, kinderjare trauma, premorbiede aanpassing, fisiese verwaarlosing, tydperk van kinderjare trauma

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LIST OF ACRONYMS / ABRREVIATIONS

ACTH	Adreno Corticotrophin Hormone
AIDS	Acquired Immune Deficiency Syndrome
APA	American Psychiatric Association
BDNF	Brain Derived Neurotrophic Factor
CHR	Clinical High Risk
COMT	Catechol-O-Methyltransferase
CH	Childhood
CRF	Case Report Form

CRH	Corticotrophin Releasing Hormone
CT	Childhood Trauma
CTQ-SF	Childhood Trauma Questionnaire – Short Form
DSM	Diagnostic and Statistical Manual of Mental Disorders
DUP	Duration of Untreated Psychosis
EA	Emotional Abuse / Early Adolescence
EEV	Eerste Episode Skisofrenie Spektrum Versteurings
EN	Emotional Neglect
FES	First-Episode Schizophrenia Spectrum Disorders
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HPA	Hypothalamic Pituitary Adrenal Axis
ICH	International Conference on Harmonisation
LA	Late Adolescence
LEC-5	Life Events Checklist
PA	Physical Abuse
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PN	Physical Neglect
PTSD	Post Traumatic Stress Syndrome
SA	Sexual Abuse
SCID	Structural Clinical Interview for DSM
SD	Standard Deviation
SFS	Social Function Scale
SOFAS	Social and Occupational Functioning Assessment Scale
SPA	Sexual and Physical Abuse
SPSS	Statistical Package for Social Sciences
TAQ	Trauma Antecedents Questionnaire
TN	Traumagenic Neurodevelopmental

CHAPTER 1
INTRODUCTION

1.1 BACKGROUND

Repeated exposure to multiple types of childhood trauma has long-lasting effects on mental health, which often persist into adulthood (Gilbert et al., 2009). Childhood trauma refers to a broad range of adverse experiences occurring during childhood and adolescence (McLaughlin, 2016). The range of serious adverse experiences, such as emotional, sexual and physical abuse, as well as physical and emotional neglect, is referred to as childhood trauma (Morgan & Fisher, 2007). According to Bernstein and Fink (1998), emotional abuse can be described as anything humiliating, threatening or demeaning towards a child's sense of worth, through verbal assaults by an older person. Physical abuse refers to as bodily assaults by an adult person on a child that poses risk or results in injury. Sexual abuse refers to sexual contact between an older person and a child younger than 18 years, including explicit coercion. Emotional neglect refers to the lack of basic emotional and psychological needs of a child, due to the failure of the caregiver to provide in nurturance, love, belonging, and support. Lastly, physical neglect refers to the failure to provide in a child's basic physical needs that includes safety, shelter, food, and when a child's safety is in jeopardy due to poor parental supervision (Bernstein & Fink, 1998).

The detrimental consequences of childhood trauma are well-known (Paolucci, Genuis & Violato, 2010). Survivors of childhood trauma are more likely to develop psychiatric illnesses such as depression and post-traumatic stress disorder (PTSD) compared to individuals without childhood trauma exposure. Approximately 45% of people who develop a psychiatric disorder in early adulthood or later are known to have a history of childhood trauma (Carey, Walker, Rossouw, Seedat & Stein, 2008; Teicher & Samson, 2016). As with other disorders, childhood trauma is also an important risk factor of schizophrenia (Varese et al., 2012). Schizophrenia affects approximately 1% of the general population (Zai et al., 2004), and is a severely disabling disorder (Geekie & Read, 2009). Many individuals living with the illness experience poor long-term functional outcomes and decreased quality of life (Geekie & Read, 2009). According to the American Psychiatric Association (APA)'s *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (5th ed.; DSM-5; APA, 2013) schizophrenia spectrum disorders "are defined by

abnormalities in one or more of the following five domains: delusions, hallucinations, disorganised thinking (speech), grossly disorganised or abnormal motor behaviour (including catatonia), and negative symptoms" (p.187). The onset of schizophrenia generally occurs between the ages of 17 and 25 (Geekie & Read, 2009). In general, individuals experience a prodromal phase prior to illness onset. During the prodromal phase, individuals experience a deviation from normal functioning, which may include changes in emotion, behaviour, and cognition. Prodromal symptoms include depressed mood, anxiety, suspiciousness, poor concentration, irritability, social withdrawal, and sleep disturbances (Khamker, 2015).

One mechanism whereby childhood trauma could increase the risk for schizophrenia lies in its adverse influence on neurodevelopment (Varese et al., 2012), in part relating to unregulated release of dopamine in the brain (Murray, Bhavsar, Tripoli & Howes, 2017). Unregulated dopamine synthesis has been detected as early as the onset of prodromal symptoms, with a gradual increase of dopamine release during the transition, into early psychosis. Animal studies found that these early neurodevelopmental disturbances result in a dopamine system that is hyper-responsive to stress during adolescence. Similar results have been reported in humans with a history of childhood trauma once exposed to adolescent related psychosocial stressors (Murray et al., 2017).

The influence of childhood trauma on mental health is particularly relevant in developing countries such as South Africa, where childhood trauma is highly prevalent (Ward, Artz, Leoschut, Kassanjee & Burton, 2018). South Africa is regarded as one of the most violent societies in the world, resulting in many children and adolescents experiencing different types of trauma. One in three young people in South Africa are sexually abused before the age of 17 (Ward et al., 2018). Three children are murdered per day in South Africa, and 44.5% of child murder victims were subjected to abuse and neglect (Mathews, Abrahams, Jewkes, Martin & Lombard, 2012). Despite constitutional legislation against child abuse in South Africa, a large number of children still suffer abuse (Richter & Dawes, 2008). Children often experience corporal punishment for minor transgressions, both at school and at home (Hecker, Hermenau, Isele & Elbert, 2014), placing them at a higher risk to suffer more severe forms of physical abuse in a violent society such as South Africa (Meinck, Cluver, Boyes & Mhlongo, 2015). In particular, child

orphans appear to be at greater risk for physical abuse (Thurman & Kidman, 2011). In South Africa, 1.37 million cases of orphaned children were reported in 2005, of which 830 000 were orphaned by Acquired Immune Deficiency Syndrome (AIDS) (Dorrington, Johnson, Bradshaw & Daniel, 2005).

Other risk factors for physical abuse by primary caregivers include parental substance and alcohol abuse (Meinck, Cluver, Boyes & Ndhlovu, 2015). Emotional abuse is also an important issue. Close relatives and primary caregivers are primarily responsible for the high rates of lifetime emotional abuse (Meinck, Cluver, Boyes & Loening-Voysey, 2015). Consequently, many children suffer physical and emotional neglect due to malnourishment, living in poor overcrowded households without running water, and poor parental supervision, while fearing for their safety due to high crime levels (Berry, Biersteker, Dawes, Lake & Smith, 2013). Neglect results from inadequate parental supervision and care associated with poverty (Hobbs & Wynne, 2002). South Africa is also known for high levels of poverty. Fifty-eight percent (58%) of children younger than nine years live under conditions of extreme poverty in South Africa (Berry et al., 2013). Childhood trauma is an important risk factor for major psychiatric disorders such as depression, PTSD and schizophrenia in South Africa (Carey et al., 2008; Seedat et al., 2009; Burns, Jhazbhay, Esterhuizen & Emsley, 2011).

1.2 PROBLEM STATEMENT AND STUDY RATIONALE

The mechanisms whereby childhood trauma contributes to the risk for psychosis and poorer treatment outcomes in first-episode patients remain unclear. Although it has been proposed that childhood trauma exerts a deleterious effect on disease risk via its effects on premorbid adjustment, findings to date have been both inconclusive and conflicting. Few studies have considered the effects of specific trauma subtypes on distinct domains of premorbid functioning across early life, and there is a scarcity of research on the timing of early life events and how it affects the relationship between childhood trauma and premorbid adjustment. The relationships between childhood trauma, poor premorbid adjustment, greater illness severity and poorer outcomes thus remain incompletely elucidated.

Premorbid adjustment refers to academic and social functioning during childhood through early adulthood, i.e. the period prior to illness onset (Cannon-Spoor, Potkin & Wyatt, 1982). Poor premorbid adjustment is an indicator of neurodevelopmental compromise, which is a proxy measure for schizophrenia (Tarbox, Brown & Haas, 2012). Poor premorbid adjustment could therefore be a risk factor for schizophrenia. It could be that early childhood trauma impairs academic and social functioning, which in turn renders individuals with a genetic predisposition towards schizophrenia more vulnerable, with a greater likelihood to develop the illness. A better understanding of the specificity of early trauma and its relationship with premorbid adjustment may assist to identify and treat at-risk individuals early on.

The relatively few studies that have explored the relationship between premorbid adjustment and childhood trauma have produced inconsistent findings, with some studies reporting an association (Schenkel, Spaulding, DiLillo & Silverstein, 2005; Conus et al., 2010; Ramsay, Flanagan, Gantt, Broussard & Compton, 2011; Tikka et al., 2012; Stain et al., 2014; Alameda, Ferrari, Baumann, Gholam-Rezaee, Do & Conus, 2015; Haahr et al., 2016; Kilian et al., 2017; Rubinstein et al., 2017), while others did not (Trauelsen et al., 2016; Chan et al., 2018). In order to understand the relationship between childhood trauma and poor premorbid functioning, it is important to consider the differential effect of early trauma type. It is proposed that abuse and neglect may be differentially related to psychosis (Myin-Germeys & van Os, 2007). Abuse refers to actual harm done to a child, whereas neglect refers to the lack of physical and emotional support (Shipman, Edwards, Brown, Swisher & Jennings, 2005). Myin-Germeys and van Os (2007) proposed that abuse is connected to psychosis via the affective pathway and neglect via the cognitive pathway. These pathways have different cognitive and clinical associations and therefore regarded as distinct pathways (Van Dam et al., 2015). More general neurodevelopmental impairment is associated with the cognitive pathway, characterized by prominent cognitive and negative symptoms. For example, individuals who are exposed to emotional neglect experience a lack of mental stimulation during childhood, which contributes to greater cognitive deficits (Myin-Germeys & van Os, 2007). Several studies have found evidence that cognitive impairment is a predictor of poorer functional outcomes in schizophrenia (Bowie & Harvey, 2006). People living with schizophrenia who were exposed to neglect during childhood are associated with more negative symptoms (Myin-Germeys & Van Os,

2007). The affective pathway is associated with a heightened stress sensitivity to daily life hassles and a disorder with an episodic course, characterised by positive and affective symptoms with a more favourable outcome. It could be that individuals who are exposed to abuse while growing up become oversensitive to subsequent stressors, resulting in heightened sensitivity to daily life stressors. Abuse in particular may result in changes of hypothalamic-pituitary-adrenal (HPA)-axis functioning, leading to altered stress responsiveness (Read, Bentall & Fosse, 2009). Individuals who suffered abuse during childhood and develop schizophrenia later in life are often likely to present with more positive and affective symptoms (Myin-Germeys & Van Os, 2007).

Then timing of first exposure to childhood trauma is another important factor to consider (Morgan & Fisher, 2007). The age of exposure to childhood trauma and multi-victimization may have a stronger association with the risk of developing psychosis compared to the type of trauma experienced (Varese et al., 2012). Exposure to trauma at specific periods of neurodevelopment may result in excessive synaptic pruning, which has been linked to schizophrenia (Schalinski & Teicher, 2015) and abnormal neurodevelopment (McLaughlin, Sheridan & Nelson, 2017). Synaptic connections of neurons that are not in regular use are “pruned” as a normal physiological process during neurodevelopment. Excessive synaptic pruning shortens the dendrite spines of the neurons, with a reduction in the density of the dendrite spines. A reduction of spine density may result in reduced white matter connectivity and cortical thinning, both associated with impaired cognitive functioning (McLaughlin et al., 2017). Despite the importance of the timing of childhood trauma exposure, only one study to date (Alameda et al. 2015) has examined whether the timing of childhood trauma moderates the relationship between childhood trauma and premorbid adjustment. The authors investigated the timing of physical and sexual abuse and its relationship with premorbid functioning. However, the timing of other types of childhood trauma, such as emotional and physical neglect and emotional abuse were not investigated (Alameda et al. 2015).

1.3 OVERALL AIMS AND SPECIFIC OBJECTIVES

The overarching aim of this study was to investigate the associations between childhood trauma and premorbid functioning, as well as the potential moderating effect of timing of trauma, in a cohort of FES patients. The trauma subtypes included physical

abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Assessment of physical abuse entailed gathering information on whether patients were hit so hard that it left bruises, or so bad that they needed to see a doctor, whether they were punished with hard objects, and whether they were physically abused (Bernstein & Fink, 1998). Emotional abuse tapped into aspects like being called names or heard hurtful things from family members, whether their parents wished they were never born, whether they felt hated, and whether they were emotionally abused (Bernstein & Fink, 1998). To gather information on sexual abuse, participants were asked whether they were touched in a sexual way, whether they have been threatened to get hurt if they do not engage in sexual acts, whether they were forced to do sexual things, whether they were molested, and whether they were sexually abused (Bernstein & Fink, 1998). Physical neglect tapped into information on whether participants had enough to eat, whether they were properly taken care of, whether their parents were to drunk or high when taking care of them, whether they had to wear dirty clothes, and whether they were taken to a doctor when they needed medical care (Bernstein & Fink, 1998). To assess emotional neglect, the participants were asked whether they felt loved as a child, whether someone in the family made them feel important, whether family members looked out for each other, whether their families felt close to each other, and whether their families were a source of strength (Bernstein & Fink, 1998).

1.4 RESEARCH HYPOTHESES AND AIMS

Aim 1: To explore the relationships between childhood trauma (overall trauma and specific trauma subtypes) and developmental periods of premorbid adjustment in individuals living with schizophrenia spectrum disorders.

Hypothesis:

- Childhood trauma will be significantly associated with poorer overall premorbid adjustment and poor premorbid functioning across multiple developmental periods.
- There will be a differential relationship between childhood trauma subtype and the specific developmental periods of premorbid adjustment.

Aim 2: To investigate whether timing of childhood trauma affects the relationship between childhood trauma and premorbid adjustment.

Hypothesis:

- Timing of childhood trauma will significantly moderate the relationship between childhood trauma and premorbid adjustment, with earlier trauma associated with worse premorbid functioning across multiple developmental periods.

1.5 THESIS STRUCTURE AND OUTLINE

The present thesis is outlined as follows. Chapter Two (2) provides the bio-psycho-social framework for the current research, with emphasis on the traumagenic neurodevelopmental model and associations with HPA-axis functioning. The literature review is provided in Chapter Three (3), which mainly focuses on the relationship between childhood trauma and premorbid adjustment in schizophrenia spectrum disorders. The study methodology is presented in Chapter Four (4), and results from the data analysis are outlined and discussed in Chapter Five (5). In Chapter Six (6), the study limitations and strengths are described, and recommendations for future research are provided as well as a general research conclusion.

CHAPTER 2
THEORETICAL FRAMEWORK

In this chapter, the theoretical framework underpinning the present research project is outlined. For this study, the traumagenic neurodevelopmental (TN) model was selected, which considers the impact of environmental stressors on brain development as part of a bio-psycho-social understanding of schizophrenia (Read, Perry, Moskowitz & Connolly, 2001). In particular, the present chapter focuses on the influence of childhood trauma on neurodevelopment, as well as the hypothalamic-pituitary-adrenal (HPA)-axis dysregulation as a biological correlate and common mechanism, which links these, factors (Read et al., 2009).

2.1 THE BIOPSYCHOSOCIAL FRAMEWORK

George Engel first described the bio-psycho-social framework in 1977 as a means of facilitating a comprehensive approach to understanding human development, functioning, and behavioural change (Melchert, 2013). Engel sought to encourage clinicians to view patients not just as biological organisms with an illness, but also as a whole with complex emotions and behaviors (Tavakoli, 2009). The bio-psycho-social model thus originated as a framework for better understanding the multilevel interactions associated with psychiatric illnesses. Multilevel interactions can be explained as subjective psychological experiences that occur in a social environment, resulting in a biological response (Carpenter, 1987). For more than twenty years, the stress-diathesis model that involves a bio-psycho-social approach, focusing on the integration of three paradigms, were used to study the aetiology of schizophrenia (Zubin & Spring, 1977; Nuechterlein & Dawson, 1984; Read et al., 2001). Patients with schizophrenia are not exposed to extraordinary amounts of stress, but rather demonstrate over-sensitivity to stressors, which are inherited genetically (Read et al., 2001). The bio-psycho-social model does not imply that childhood trauma is the only aspect that plays a role in the aetiology of schizophrenia. Instead, it suggests childhood trauma might contribute to disease risk either independently, or via specific interactions with peri-natal and genetic risk factors (Read et al., 2001).

The bio-psycho-social model includes three categories, i.e. the biological, psychological, and social dimensions (Tsoi, Hunter & Woodruff, 2008). Barker, Gumley, Schwannauer and Lawrie (2015) proposed an integrated bio-psycho-social framework to study the link between childhood trauma and the development of psychosis. Barker et al. (2015) suggested that researchers explore pathways linking biological brain changes to childhood trauma. A biological driven (genetic) predisposition towards developing psychosis has been described as interacting with environmental factors, ultimately leading to psychosis (Zubin & Spring, 1977). The interaction between environmental factors (such as childhood trauma) and a genetic predisposition towards psychosis could increase the risk for illness emergence later in life (Barker et al., 2015). Hyper-activation of the HPA-axis as a result of childhood trauma is one possible pathway to psychosis, mediated by epigenetic processes that include altered methylation of brain-derived neurotrophic factor (BDNF), oxytocin and glucocorticoid receptor genes (Roth, Lubin, Funk, & Sweatt, 2009). Importantly, oxytocin has been associated with attachment security (Buchheim et al., 2009).

A psychological framework provided by attachment theory can be useful in integrating interpersonal experiences, social cognition, and the regulation of affect that develops because of psychological distress (Mallinckrodt, 2000). Individuals with a history of infant-caregiver interactions that resulted in fear of the caregiver tend to develop a disorganised attachment style (Cicchetti & Toth, 1995), that can evolve into an insecure-avoidant attachment style, with an increased risk to develop psychosis (Berry, Barrowclough & Wearden, 2007). Extended separation, neglect, abuse, and loss impose a threat to the integrity of the attachment system (Bowlby, 1982). Attachment insecurity because of exposure to childhood trauma can be changed by means of psychological intervention (Mallinckrodt & Wei, 2005). The development of mentalisation skills is disrupted in the face of negative interpersonal experiences, as evident in individuals with an insecure-avoidant attachment style and patients with schizophrenia (MacBeth, Gumley, Schwannauer & Fisher, 2011). Attachment difficulties may therefore be ameliorable through mentalisation–based therapy (Neville, 2014).

2.2 SCHIZOPHRENIA AS A NEURODEVELOPMENTAL DISORDER

Historically schizophrenia was considered as a degenerative disorder, and now recognized as a developmental disorder with aspects of degeneration. The illness has characteristics of a neurodegenerative disease, due to the progressive nature of the illness, but with very subtle indications of underlying neuropathology (McClure & Lieberman, 2003). So far, no cellular or molecular processes have been identified that are linked to this neurodegeneration. The onset of deterioration in occupational and cognitive functioning, which begins in adolescence and continues after the first five years of illness onset, suggests that limited neurodegenerative progression takes place (McClure & Lieberman, 2003). Therefore, to study neurobiological processes during the prodromal phase of schizophrenia is deemed important. Antipsychotic treatment also suppresses the underlying pathophysiology of schizophrenia. It is however not clear whether structural changes of the brain take place prior to onset of schizophrenia or later. Evidence from post-mortem studies suggests the limited neurodegenerative processes that take place in schizophrenia do not include cell death (McClure & Lieberman, 2003). However, the idea of the illness as a purely neurodegenerative disorder remains controversial. The illness is immensely complex, with great heterogeneity. There are various factors other than the illness that may influence deteriorating neurocognitive and psychosocial changes over time, including environmental factors, antipsychotic use, and substance use. That being said, there may be illness-related degenerative processes involved in a subset of patients living with schizophrenia. For example, Knoll et al. (1998) found progressive premature atrophy of brain tissue in a subset of patients, resulting in the failure to maintain neuron membranes phospholipids, enlargement of the cerebral ventricles, as well as early neurophysiological brain changes.

In contrast to the neurodegenerative model, the neurodevelopmental model postulates that, although clinical symptoms of schizophrenia mainly present during late adolescence and early adulthood, subtle deficits may be present during early development, which increase the risk for the development of psychosis later in life (Schmidt-Kastner, van Os, Esquivel, Steinbusch & Rutten, 2012). According to the neurodevelopmental model, schizophrenia results from the disruption of early brain development due to abnormal genetic and/or epigenetic processes. These

processes include perinatal, intrauterine and environmental events, as well as neurobiological maturational processes (McClure & Lieberman, 2003). Strong evidence exists for the presence of neurocognitive, neuro-motor, and neurobehavioral disruptions prior to the onset of schizophrenia (Schenkel & Silverstein, 2004). Furthermore, the presence of enlarged ventricles, decreased cortical grey matter, and decreased hippocampal volumes prior to illness onset are evidence of developmental neuropathology in support of the neurodevelopmental model (McClure & Lieberman, 2003).

In the mid 1980's, the neurodevelopmental model became prominent amongst researchers in the United States of America as well as the United Kingdom, who focused on abnormal developmental histories of patients with schizophrenia (Murray et al., 2017). Minor physical and neuro-motor anomalies during childhood of patients diagnosed with schizophrenia were identified, which the degenerative model failed to explain. This led to many studies investigating pre-schizophrenic children (Murray et al., 2017). A British Cohort study reported on the presence of impaired cognitive functioning, speech delays, minor neuro-motor abnormalities, and alienation from society by the age of eight years. These children with schizophrenia-like symptoms gradually fell behind their normal peers during their development from infancy to adolescence. According to the neurodevelopmental model, psychosis is the result of excessive synaptic pruning during adolescence (Murray et al., 2017). Synaptic pruning is a normal physiological process, whereby synaptic connections that are not in regular use are "pruned". However, excessive pruning may result in an over-reduction of dendrite spine density (McLaughlin et al., 2017). A recent genetic study found that C4 genes, which constitute a risk factor for schizophrenia, are implicated in excessive synaptic pruning (Sekar et al., 2016), in support of the neurodevelopmental model.

2.3 THE TRAUMAGENIC NEURODEVELOPMENTAL MODEL

The TN model focuses on both biological and psychological processes involved in the development of schizophrenia. It proposes that heightened stress sensitivity observed in schizophrenia is not only due to genetic factors. In fact, early trauma may be a causative factor of stress sensitivity, either through its interaction

with genetic factors, or independently. Prior to the TN model, it was proposed that heightened stress sensitivity is caused by biological factors only, and that the environment played a non-significant role (Read et al., 2001). However, this view was challenged due to the similarities found in neurobiological abnormalities when comparing patients with schizophrenia and individuals with a history of childhood trauma (Limosin, 2014). In particular, both groups showed an overactive HPA-axis, and abnormalities in brain structure and neurotransmitters, such as dopamine (Read et al., 2009).

According to the TN model, childhood trauma that occurs early enough, or entails a significant degree of severity, predisposes towards neurodevelopmental abnormalities underlying the heightened responsiveness to stressors characteristic of schizophrenia. The TN model proposes that the prolonged neurobiological effects of childhood trauma cause biochemical and neurological abnormalities in patients with schizophrenia (Read et al., 2001). A study comparing patients with a first episode of schizophrenia, with and without a history of childhood emotional abuse suggests a greater HPA-axis dysregulation in the abused group. The regulation of the HPA-axis was measured through cortisol levels with a significant association between early-life parental practices as well as childhood sexual abuse (Read et al., 2009).

2.4 DYSREGULATION OF THE HPA-AXIS

The HPA-axis (see Supplementary Figure1 in Appendix A) is the central stress response system, and involves the central nervous system and the endocrine system (Philips et al., 2006). When people experience stress, two hormonal systems are activated. The first hormonal response acts immediately and mediates the sympathetic nervous system, resulting in the release of noradrenaline and adrenaline into the bloodstream, known as the “fight-or-flight “reaction to stress. The second hormonal response acts much slower over an extended period and is mediated by the HPA-axis. The initial response of the HPA-axis is initiated by neurons in the nucleus of the hypothalamus, which release corticotrophin releasing hormone (CRH), signaling the pituitary gland to release adreno-corticotropic hormone (ACTH), which in turn stimulates the adrenal glands to synthesize and

release glucocorticoids, including cortisol. Once the stressor is removed, through negative feedback of glucocorticoids on the pituitary gland, hypothalamus, prefrontal cortex, and hippocampus, the production of CRH and ACTH is reduced, and homeostasis is restored. Glucocorticoids are therefore responsible for many of the behavioral and physiological responses to intrinsic and external stressors (Romeo, 2013). Over the course of prolonged exposure to elevation of glucocorticoid levels, the hippocampus is damaged, which reduces the ability of the stress response system to return to a state of homeostasis. A vicious cycle of events known as the "glucocorticoid cascade" then takes place (Philips et al., 2006).

Adolescence also goes hand in hand with many neuro-endocrinological changes, which include an increase in gonadal hormones associated with puberty, with a subtle shift in HPA-axis function. Glucocorticoid and ACTH levels demonstrate more abrupt shifts once exposed to stress in adolescence, especially during late compared to early adolescence and late childhood. The prefrontal cortex, amygdala and hippocampus, which undergo maturity during adolescence, are particularly sensitive to stress. As a result, exposure to extended periods of high levels of glucocorticoids due to stress gives rise to a heightened sensitivity to stressors that may lead to maladaptive behavioral development (Romeo, 2013).

Prolonged exposure to early trauma could result in the HPA-axis failing to restore homeostasis (Gjerstad, Lightman & Spiga, 2018). When the HPA-axis fails to properly restore homeostasis by not releasing cortisol, hypersensitivity to stress and the release of cytokines occur (Gispen-de Wied, 2000). The link between hypersensitivity of the HPA-axis and schizophrenia is well-established (Bradley & Dinan, 2010). Many patients with schizophrenia are hypersensitive to relative minor stressors such as daily life hassles, which is predictive of relapse susceptibility (Gispen-de Wied, 2000). Evidence of a blunted cortisol response has been found in chronic schizophrenia patients as well as individuals at clinically high-risk (CHR) for psychosis (Thompson et al., 2007). Thompson et al. (2007) studied the cortisol levels in individuals at CHR for psychosis. The authors found that CHR for psychosis individuals who went onto develop chronic psychosis had lower cortisol levels than the non-transition high-risk individuals. Blunted cortisol release in schizophrenia may

be partially related to cognitive deficits known to characterize the illness (Thompson et al., 2007).

In conclusion, converging lines of evidence support the notion that schizophrenia is a disorder of abnormal neurodevelopment. In addition to biological factors, it is now appreciated that psychological and social factors also contribute to or exacerbate abnormal neurodevelopment during adolescence, which predisposes towards the development of schizophrenia. In this context, childhood trauma has been associated with increased risk of developing schizophrenia, due in part to its effects on neurodevelopment. In particular, childhood trauma is thought to adversely affect functioning of the HPA-axis, which is associated with increased stress sensitivity. In conclusion, the neurodevelopmental model constitutes an appropriate framework for researchers to explore the contribution of environmental stressors including childhood trauma to the development, presentation and outcome of schizophrenia.

CHAPTER 3
LITERATURE REVIEW

3.1 BACKGROUND

Mental health research has mainly focused on studying early trauma in relation to five inter-related factors, namely genetics, patient outcomes, cognitive functioning, brain morphology, and premorbid adjustment. Although the focus of the current study was on the relationship between childhood trauma and premorbid adjustment in schizophrenia spectrum disorders, a brief overview of the other factors within psychotic disorders and at clinical high-risk (CHR) populations were provided to contextualize the dissertation topic. Firstly, literature on the relationship between childhood trauma and genetics was provided, followed by childhood trauma and patient outcomes. Childhood trauma and cognition as well as brain abnormalities also received attention. Lastly, studies focusing specifically on childhood trauma and premorbid functioning were presented.

3.2 CHILDHOOD TRAUMA AND GENETICS

Previous studies have sought to address whether the interaction between childhood trauma and genetic factors affects clinical and cognitive outcomes in patients living with a psychotic disorder. In a study by Green et al. (2014), the authors found that patients with schizophrenia who were Catechol-O-methyltransferase (COMT) Met-allele carriers and had a history of childhood trauma were more likely than Met-allele carriers without trauma histories to experience greater symptom severity. This was the case for COMT Met-allele carriers with a history of physical abuse and emotional neglect. Interestingly, COMT Met-allele carriers with a history of physical abuse had better executive functioning than those Met-allele carriers without this type of abuse (Green et al., 2014). When comparing patients who were carriers of the serotonin transporter gene 5-HTTLPR promoter polymorphism and experienced a history of childhood trauma, those with the short allele had worse performance across various cognitive domains compared to those with the long allele (Aas et al., 2012). Patients with schizophrenia and bipolar

disorder with a history of childhood trauma had a shorter telomere length. A shorter telomere length is associated with accelerated aging and brain volume abnormalities. When comparing the telomere length of patients and healthy controls, patients had a shorter telomere length. However, the differences in telomere length disappeared when controlling for the effect of a history of childhood trauma. This finding suggests a history of early trauma attributed to between group differences in telomere length. The authors found that telomere length was not associated with reduced brain volume in patients (Aas et al., 2019).

The interactions between genetic and environmental factors implicated in childhood trauma are often unclear. However, patients exposed to childhood trauma who were also carriers of the COMT Met-allele experienced greater symptom severity (Aas et al., 2012). Patients with a history of childhood trauma also displayed a shorter telomere length compared to healthy controls, which could indicate accelerated brain ageing (Aas et al., 2019).

3.3 CHILDHOOD TRAUMA AND OUTCOME

Studies focusing on the relationship between childhood trauma and patient outcomes have primarily studied the association between early trauma and psychopathology, psychosocial functioning, treatment adherence, and health service use.

Patients with a history of childhood trauma likely have a distinct clinical profile. Exposure to childhood trauma has been related to a higher incidence of depressive (Duhig et al., 2015) and dissociative symptoms (Greenfield, Strakowski, Tohen, Batson & Kolbrener, 1994). Patients with a first onset of psychosis with a history of childhood physical and sexual abuse presented with more severe dissociative symptoms, but not necessarily with more severe overall psychotic symptoms (Greenfield et al., 1994). Dissociation may serve as a defence mechanism against prolonged traumatic stress, and includes shutting down of motor, sensory, and speech systems (Schalinski & Teicher, 2015). Unlike adults, children are more likely to use dissociation as a means to cope with high anxiety-provoking incidents (Schauer & Elbert, 2010). This “default” coping mechanism could be carried into adulthood, thus providing an explanation for why patients with a history of childhood

trauma are more likely to experience dissociation. Furthermore, a history of childhood trauma has been correlated with slower improvement in symptoms over time (Pruessner et al., 2019). However, the relationship between childhood trauma and psychopathology is not linear and it is likely that multiple pathways link childhood trauma with psychopathology (Isvoranu et al., 2017).

Isvoranu et al. (2017) identified three general psychopathologies (anxiety, poor impulse control, and motor retardation) as mediators of the relationship between childhood trauma and the positive and negative symptom domains of schizophrenia. Positive symptoms refer to a loss of touch with reality, and include delusions, hallucinations, formal thought disorder, and agitation, among others (National Institute of Mental Health [NIMH], 2003). Negative symptoms refer to disrupted behaviours and emotions, and include symptoms such as reduced emotional expression, reduced communication, reduced feelings of pleasure, and difficulty to initiate and sustain activities (NIMH, 2003). Anxiety mediated the relationship between childhood trauma and positive symptoms, such as paranoia, delusions, and hallucinations. In comparison, poor impulse control mediated the relationship between childhood trauma and positive symptoms, such as grandiosity, hostility, and excitement. Lastly, motor retardation mediated the relationship between childhood trauma and negative symptoms (Isvoranu et al., 2017).

A link between poor social functioning and childhood trauma has also been reported. Patients with schizophrenia with a history of childhood trauma showed a slower improvement in psychosocial function over time (Davidson, Shannon, Mulholland & Campbell, 2009). A history of childhood trauma may also affect inter-personal relationships, with some evidence suggesting that patients with a history of physical abuse are more likely to not be in a romantic relationship (Trotta et al., 2016). A history of childhood trauma in patients with a psychotic disorder has also been associated with poorer treatment adherence and more frequent use of mental health services (Lecomte et al., 2008). Parental separation has also been associated with poor compliance to antipsychotic treatment and compulsory hospital admissions (Ajnakina et al., 2018) as well as longer hospitalization (Trotta et al., 2016). Similarly, parental death has also been associated with compulsory hospital admissions and institutional foster care with longer inpatient hospital stays (Ajnakina et al., 2018).

Therefore, childhood trauma may be a risk factor for undesirable outcomes in patients with schizophrenia, such as poor psychosocial functioning, symptoms of dissociation, depressive symptoms, frequent hospital admissions, and poorer adherence to treatment.

3.4 CHILDHOOD TRAUMA AND COGNITION

Cognitive deficits are a core feature of schizophrenia and precede the onset of the illness, as reflected by poor school performance, among others (Kahn & Keefe, 2013). It could be that these cognitive impairments associated with trauma exposure in childhood persist into adulthood (Perez & Widom, 1994) and have a lasting effect on cognitive functioning in adult psychiatric patients. Indeed, studies have found that patients with a history of childhood trauma have greater cognitive impairment in episodic narrative and working memory (Shannon et al., 2011).

Childhood neglect has been associated with poorer verbal learning and social cognition in patients, while neglect was identified as a predictor of attention/vigilance and social cognition in controls (Kilian et al., 2018). Social cognition refers to cognitive processes which underlie the processing of social interactions, such as social perception, emotion processing, and theory of mind (Green et al., 2008). Childhood abuse was not found to be a predictor of cognitive impairments in either controls or patients. In this particular study, the effect of childhood neglect on social cognition seems to not be illness-specific (Kilian et al., 2018).

The relationship between childhood trauma and cognition is likely influenced by biological sex (Aas et al., 2011). Poor cognitive performance was reported in male patients with affective psychosis with a history of childhood trauma; however, within the same population, no association between cognition and childhood adversity was observed in female patients or controls (Aas et al., 2011). Sex-specific effects were reported in a study where healthy male and female controls were exposed to a psychosocial stressor, the male controls had an increased cortisol level with poor cognitive performance, but this was not evident in the female controls (Wolf, Schommer, Hellhammer, McEwen& Kirschbaum, 2001).There is strong evidence that a history of childhood trauma in males had increased cortisol responses

compared to no cortisol responses in women with the same history, suggesting a gender-specific reactivity to the HPA-axis (Pesonen et al., 2010).

In a sample with an early onset of psychosis patients exposed to childhood trauma, women performed better in processing speed and verbal learning than men. However, both sexes with a history of childhood trauma presented with poorer social cognition compared to healthy controls (Garcia et al., 2016). Poorer attention, vigilance, and mentalising skills were found to mediate the relationship between childhood neglect and disorganisation, specifically in men with psychotic disorders. Poor working memory also seemed to mediate the relationship between childhood abuse and excitement, disorganisation, as well as emotional distress in men (Mansueto et al., 2019).

Another important aspect of cognition that was extensively observed in patients with schizophrenia is integration deficits, which refer to as grouping, object recognition, perceptual closure, reading, or face processing (Butler, Silverstein & Dakin, 2008). Patients with schizophrenia struggle with contour integration because they find it difficult to coordinate complex contextual interactions (Keane et al., 2012). Visual integration impairment has been associated with poor premorbid functioning, disorganised psychotic symptoms, and childhood trauma (Butler et al., 2008). Schenkel et al. (2005) found dysfunctional perceptual grouping in patients with a history of childhood trauma was evident; however, this association was not observed in patients with no history of childhood trauma. In particular, patients with a history of abuse experienced delayed contour integration ability, with perceptual grouping function at a level of age 5-6 years (Schenkel et al., 2005).

A history of childhood trauma therefore explains some of the variance in cognitive functioning observed in patients living with schizophrenia. However, other potentially confounding factors are not always taken into account when studying the relationship between childhood trauma and cognitive functioning. For example, deprivation of cognitive stimulation and basic physical needs may result in abnormal prefrontal cortex function with neurocognitive development compromise (Sheridan et al., 2012), which could impair cognitive functioning. Maternal malnutrition has a negative impact on the developing foetus, with risk for specific cognitive deficiencies during childhood. The normal physiological decline between the ages of 13 and 15

years in selective attention controlled by the prefrontal cortex, initiates earlier in the case of early gestation nutrient deprivation (De Rooij, Wouters, Yonker, Painter & Roseboom, 2010). The brain is vulnerable to malnutrition during sensitive periods of development, including the period from the second trimester of pregnancy up to the age of two years, with irreversible long-term cognitive and behavioural consequences (Galler & Barret, 2001). Delays in language acquisition and intellectual impairment have been reported in children with a history of malnutrition. Cognitive impairment due to malnutrition during childhood can continue into adulthood. These cognitive impairments can improve with iron supplementation and enriched educational programmes, the latter not always being available to the poor (Brown & Pollitt, 1996).

3.5 CHILDHOOD TRAUMA AND BRAIN ABNORMALITIES

A history of childhood trauma may partly explain brain alterations associated with psychosis. Childhood trauma has been associated with reduced white matter integrity (Benedetti et al., 2014; Asmal et al., 2018) (indicative of microstructural brain tissue changes), as well as reduced grey matter volume (Barker et al., 2016) (indicative of macro structural brain tissue changes) in patient and at-risk cohorts.

Various studies have found differences in white matter integrity when comparing patients with a psychotic disorder with controls, and some of these differences could be due to a history of childhood trauma. A relationship has been found between axial diffusivity, a measure of white matter integrity, and childhood trauma in patients with bipolar disorder (Benedetti et al., 2014). In comparison, a relationship has also been found between another measure of white matter integrity, fractional anisotropy, and childhood trauma in patients with a first-episode of schizophrenia spectrum disorders (Asmal et al., 2018). Furthermore, there is likely a relationship between childhood trauma and cortical grey matter surface areas in individuals with a familial risk for schizophrenia. However, it should be noted that in the same population, childhood trauma did not affect cortical thickness (Barker et al., 2016), which is a measure of changes in grey matter volume (Fischl & Dale, 2000), associated with the pathophysiology of schizophrenia (Kwon et al., 1999).

It is likely that the interactive effect of illness and non-illness related factors could lead to the development of schizophrenia, given that similar brain abnormalities are also found in the general population. For example, children whose nutritional needs are not met during sensitive periods of neurodevelopment could suffer brain alterations during early development (Ednorog et al., 2012). Substance abuse during pregnancy has also been associated with brain alterations in infants (Behnke & Smith, 2013).

3.6 CHILDHOOD TRAUMA AND PREMORBID ADJUSTMENT

In order to provide a contextualized understanding of the relationship between childhood trauma and premorbid adjustment in first-episode schizophrenia spectrum disorders, an overview of studies assessing the relationship in different samples will be presented.

3.6.1 General population studies

Poor social and academic skills have been reported among individuals exposed to childhood trauma in the general population (Wood, 2016). Children exposed to childhood trauma have a higher risk for encountering behaviour problems, social and learning difficulties, including the possibility to develop a chronic mental health disorder (Wood, 2016). A chronic mental health disorder may result in lifetime social and academic difficulties, with fewer opportunities for employment, educational achievement, and healthy social integration (Larson, Chapman, Spetz & Brindis, 2017). It was suggested that children with histories of prolonged childhood trauma undergo structural changes of the brain due to hyper-vigilance to potential threats because childhood trauma victims primarily focus on survival (Ford, 2005). These brain changes have a negative impact on learning, attention, and memory capacities (Ford, 2005). These children have difficulties with processing of sensory information and therefore struggle to make sense of new information. They often suffer speech problems due to poor parental stimulation and inadequate resources (Pascoe, Wood, Duffee & Kuo, 2016), which makes it difficult for them to understand complex stories and situations, resulting in poor reading and writing skills (Streeck-Fischer & van der Kolk, 2000). These children are more likely

to fall behind their normal peers, often repeating school grades, and ending up in special needs education (Shonk & Cichetti, 2001). Childhood trauma may also have a negative impact on school performance of adolescents (Sladea & Wissowb, 2007). Poor academic achievement during middle and high school together with poor interpersonal skills are associated with lower income employment in adulthood (Cawley, Heckman & Vytlacil, 2001).

The deleterious effect of childhood trauma also extends to include social functioning, as well as peer and teacher relationships (Van der Kolk, 2003). Interpersonal relationships start to develop in early childhood and gains emotional significance depending on the quality of relationships with significant others (i.e. parents, teachers, peers). The sense of self is a trajectory of these interpersonal relationships. Dysfunction in the development of the self, inevitably determines an individual's long-term social functioning (Cole & Putnam, 1992), i.e. children subjected to violence often isolate themselves from social situations because they find it difficult to read social cues (Van der Kolk, 2003). Children exposed to physical abuse were found to have poor intimate relationships with their peers, because they tend to interact in an aggressive or negative way (Margolin & Gordis, 2000). Children with a history of childhood trauma seem to be suspicious of others, and struggle to trust people. They doubt the predictability and reliability of interpersonal relationships with their teachers and peers (Van der Kolk, 2003). Children and adolescents with childhood trauma histories do not trust authority figures, because their experiences with authority figures have not been trustworthy and also not safe (Van der Kolk, 2003). They tend to view rules and regulations as punishment therefore, constantly get caught up in school discipline violations and potential re-traumatization (Streeck-Fischer & van der Kolk, 2000).

3.6.2 At risk populations

People identified as high risk for developing psychosis are those with a mental disorder but not yet psychotic, a known developmental delay, and a known organic reason to be classified as high-risk (Yung et al., 2008). Tikka et al. (2012) reported an association between physical neglect, emotional abuse and poorer premorbid adjustment during late adolescence, as well as poorer general premorbid adjustment

in a sample at CHR for psychosis, but not in control subjects. A non-significant association between emotional abuse and poorer premorbid adjustment in early adolescence and adulthood was also seen in the CHR group. Physical neglect, emotional neglect, and emotional abuse were associated with an interruption in school attendance, impaired social-personal adjustment, and a poorer global assessment of highest level of functioning in the CHR group. Sexual abuse also demonstrated an association with a poorer score on the social-personal item of the premorbid adjustment scale (PAS) for the CHR group (Tikka et al., 2012).

Rubinstein et al. (2017) investigated the characteristics of premorbid impairment by studying premorbid archival data obtained retrospectively in male participants who were later diagnosed with a schizophrenia spectrum disorder. The quantitative data as well as qualitative interviews with these participants at the age of 17 were all performed prior to disease onset. In their mixed method study, quantitative and qualitative data were analysed and compared to premorbid data of healthy controls. Family problems, adaptation difficulties, and poor general health were reported among the group who later developed a psychotic disorder. An important strength of the aforementioned study was that all assessments were blinded to outcome because it was performed prior to illness onset (Rubinstein et al., 2017).

3.6.3 Chronic schizophrenia patient samples

Increased academic difficulties, poorer peer relationships, poorer educational attainment, and an earlier age of a first psychotic breakdown were associated with a history of childhood trauma in a chronic schizophrenia spectrum disorder sample (Schenkel et al., 2005). A significant association was found between the severity and frequency of childhood trauma and the development of later psychopathology. It was further found that multiple types of trauma had no significant differential impact on premorbid functioning, compared to one type of trauma. Premorbid cognitive impairment was evident in the group with a history of childhood trauma, regardless of how many trauma types they experienced during childhood (Schenkel et al., 2005).

In a cross-sectional study conducted by Chan et al. (2018), the authors included patients with chronic schizophrenia, who were divided into three premorbid

groups: (i) cluster I, patients with normal premorbid academic and social functioning (*n*= 28); (ii) cluster II, patients with impaired academic functioning but normal social functioning (*n*= 15); and (iii) cluster III, patients with impaired social and academic functioning (*n*=13). No relationships were found between childhood trauma and premorbid adjustment across the three groups. However, the participants from Cluster III were exposed to more severe childhood emotional neglect and suffered more negative symptoms (Chan et al., 2018).

3.6.4 First-episode schizophrenia patient samples

Studies conducted in first-episode samples are summarized in Table 1 provided at the end of this chapter. In a study conducted by Conus et al. (2010), poor premorbid functioning was associated with a history of physical and sexual abuse in patients with a first-episode of psychosis and schizoaffective disorder. Ramsay et al. (2011) reported significant correlations between childhood trauma, premorbid psychosocial problems and educational achievements in a first-episode psychosis sample with a history of high levels of childhood trauma exposure (Ramsay et al., 2011). Stain et al. (2014) found that childhood trauma (all types) correlated with poorer premorbid social functioning during childhood, early and late adolescence in a first onset of psychosis sample. An association between childhood trauma and poorer premorbid academic functioning was also evident during early adolescence. Childhood trauma was also a significant predictor of adult social functioning. Then, 45% of the patients who reported childhood trauma were also exposed to trauma during adulthood. It was therefore concluded that childhood trauma contributed to poor interpersonal skills in general, posing a risk for adult interpersonal violence, due to poor choices of partners (Stain et al., 2014).

In a study by Alameda et al. (2015) patients with a first onset of psychosis with or without a history of sexual and/or physical abuse (SPA) were divided into three groups: (i) Early-SPA patients before the age of 11 years; (ii) Late-SPA patients between the ages of 12 and 15 years; and (iii) Non-SPA patients with no history of sexual and/or physical abuse. Age of trauma exposure was a modulator of functional outcome, in other words age of childhood trauma exposure was a modulator between childhood trauma and global functioning. At baseline, the Early-

SPA group had poorer premorbid global functioning, poorer childhood social functioning, and poorer early adolescent social functioning, compared to the Non-SPA group (Alameda et al., 2015). There were no significant associations found between the Early and Late-SPA groups in any of the academic domains of premorbid functioning, compared to the Non-SPA group. Concerning the Global Assessment of Functioning Scale (GAF) and the Social and Occupational Functioning Assessment Scale (SOFAS) scores, indicative of social functioning at baseline, there were no significant associations between the Early and Late-SPA groups, compared to the Non-SPA group (Alameda et al., 2015). At all the follow-up time points, significantly poorer GAF and SOFAS scores were found in the Early-SPA group compared to the Non-SPA group. No significant differences were found in the GAF and SOFAS scores between the Late-SPA group and the Non-SPA group. Furthermore, in comparison with the Non-SPA group, the Early-SPA group showed impaired social functioning despite treatment, whereas the Late-SPA group responded to treatment and demonstrated improved social functioning over time (Alameda et al., 2015).

In a study by Haahr et al. (2016), childhood trauma was reported by 50% of patients with a first onset of psychosis, while one third reported exposure to childhood trauma before the age of 18. Women reported higher incidences of sexual abuse, emotional, and physical maltreatment as well as physical assault, compared to the men. Significant associations between premorbid adjustment, duration of untreated psychosis (DUP) and early trauma (sexual, emotional, and physical abuse) have also been reported. No associations were found between childhood trauma and level of education, clinical symptomatology at baseline, or comorbid substance use. Early traumatic experiences were thought to be the reason for delayed help-seeking behaviour in patients (Haahr et al., 2016). In contrast, no association between severe childhood trauma and any of the premorbid trajectories in a first-episode affective psychosis sample were found. However, individuals with a history of more trauma reported on more current alienation from family members, including lower rates of perceived support during childhood. A protective factor against childhood trauma was identified as peer support, which lowered the risk for psychosis with 10% (Trauelsen et al., 2016).

Kilian et al. (2017) found that physical abuse is associated with poorer academic functioning from childhood to late adolescence in a first-episode psychosis sample. Sexual abuse was associated with poorer social functioning during early and late adolescence. Physical neglect had a significant relationship with poorer premorbid academic adjustment during childhood and early adolescence, as well as poorer social premorbid adjustment during early adolescence. Emotional neglect was not associated with premorbid social adjustment, but had a significant association with poorer academic premorbid functioning throughout adolescence. Emotional abuse showed a significant correlation with poorer academic premorbid adjustment in childhood. In conclusion, there were widespread associations between different trauma subtypes and academic as well as social premorbid functioning, across various developmental stages, in patients with schizophrenia (Kilian et al., 2017). Other risk factors of interest were obstetric complications, substance abuse, a family history of psychiatric disorders or schizophrenia, and neurological soft signs. It was concluded that the association between sexual abuse, overall trauma and premorbid academic functioning in childhood is moderated by neurological abnormalities. In support of the neurodevelopmental hypothesis, an explanation of these findings is that childhood trauma plays a role in impaired neurodevelopment that manifests as poor premorbid adjustment, as a precursor of psychosis onset (Kilian et al., 2017). However, Kilian et al. (2017) did not examine the timing of early life adversity as a specific focus of their study. The authors (Kilian et al. 2017) also recommended a replication of these findings in a larger representative sample. The present study focused on a response to gaps, mentioned in the literature.

In summary, different trauma types appear to have different effects on premorbid adjustment trajectories. However, previous studies, except for one (Alameda et al., 2015), did not investigate the moderating role of timing of childhood trauma. This is a significant limitation in the literature. Furthermore, some studies did not account for the influence of other factors that could affect the relationship between childhood trauma and premorbid adjustment. One factor that could play a role is DUP. Patients with a longer DUP often have a poorer prognosis (Loebel et al., 1992). DUP has also been linked to poorer social functioning (Barnes et al., 2008). Barnes et al. (2008) re-evaluated social functioning in a one-year longitudinal study

of first-episode patients using the Social Function Scale (SFS), which was specifically designed to evaluate social functioning in schizophrenia. An association between poorer overall social functioning and a longer DUP was found, independent of positive symptoms. However, there could be various factors other than a history of childhood trauma that could influence DUP. For example, in settings such as South Africa many people are unable to easily access mental health services. For one, South Africa has 11 official languages. However, mental health professionals are mostly only proficient in Afrikaans and/or English, forcing them to rely on informal interpreters, whereby running the risk to misinterpret signs and symptoms of psychiatric illnesses (Swartz & Kilian, 2014). Another barrier includes transportation to mental health services (Bruwer, Sorsdahl, Harrison, Stein, Williams & Seedat, 2011).

Another factor is age of illness onset. Larsen et al. (2004) found that patients with a later age of illness onset reported better premorbid functioning. It seems that they were socially more integrated, less reluctant to seek help, and more knowledgeable about available health services. It was also found that late onset of psychosis occurred predominantly among female patients that were more likely exposed to severe childhood trauma (Golay et al., 2017). Sex could also influence the relationship between childhood trauma and premorbid adjustment. It is suggested that women diagnosed with schizophrenia presented with overall better premorbid functioning than men. Selectively, women are often also less impaired concerning social engagement and social role functioning compared to men (Shtasel, Gur, Gallacher, Heimberg & Gur, 1992). One possible reason for this could be that women have higher levels of oxytocin. Seltzer, Ziegler, Connolly, Prososki and Pollak (2014) reported that when compared to boys, girls subjected to physical abuse had increased levels of oxytocin. Oxytocin is a hormone associated with social functioning in adulthood (Pierrehumbert et al., 2010). Adults with a history of childhood trauma suffer a dysregulation of the oxytocin hormone that in turn gives rise to poor social relationships (Snowdon et al., 2010). A complex interaction between oxytocin and the HPA-axis takes place, oxytocin suppresses the stress response resulting in promotion of social relationships and the development of trust (Heinrichs & Domes, 2008). In humans, oxytocin is also associated with certain

cognitive functions, such as facial recognition and working memory (Cochran, Fallon, Hill & Frazier, 2013). In patients with schizophrenia, oxytocin might play a role in cognitive deficits (Nuechterlein, Ventura, Subotnik & Bartzokis, 2014). In addition, administering intranasal oxytocin has been shown to improve facial recognition in patients with schizophrenia (Averbeck, Bobin, Evans & Shergill, 2011).

In summary, the mechanisms whereby childhood trauma contribute to poor premorbid adjustment and increase the risk for developing schizophrenia are not clear. In order to address this gap in the literature the main objective of this study was to take a closer look at the associations between childhood trauma (trauma sub-types and overall trauma) and the different domains of the developmental periods of premorbid adjustment in schizophrenia spectrum disorders.

The secondary objective was to investigate whether timing of childhood trauma moderates the relationship between childhood trauma and premorbid adjustment.

Table 1. Details of sample characteristics pertaining to childhood trauma and premorbid adjustment in first-episode psychosis samples

Study	Sample Characteristics	Sample Size	Follow-up period (months)	CT Measures	Outcome Measures	Study Aim
Alameda et al., 2015	Early onset of psychosis Cambridge University	*N*=225	36	TIAT	GAF SOFAS PAS	Aimed to look at the type of trauma and the age at the time of first exposure to sexual and/or physical abuse (SPA) in association with premorbid adjustment and global functioning
Conus et al., 2010	First-episode affective psychosis or schizoaffective disorder Australia	*N*=22		CDRFI LMS LEQ	PAS K-SADS-PL GBI ASI GAF	To investigate the premorbid characteristics of patients with a history of childhood adversity

Haahr et al., 2016	First-episode of psychosis Denmark	*N*=191	60	BBTS	Clinical presentation assessments	To study the trauma types and its association with premorbid adjustment in a first-episode psychosis sample. The clinical presentation of the participants at baseline, in association with different kinds of trauma were also explored
Kilian et al., 2017	First-episode schizophrenia spectrum disorders South Africa	Patients (*n*=77) and matched controls (*n*=52)		CTQ-SF	PAS NES	The study looked at specific types of traumas to determine whether there is a differential relationship between trauma type and premorbid adjustment. An exploration of other risk factors potentially moderating the relationship

						between premorbid adjustment and early childhood adversity were also assessed
Ramsay et al., 2011	First-episode psychosis, predominantly men inpatients America	*N*=61		CTQ-SF TEC	LSUR SAPS SANS Social and academic functioning through interview	An investigation into the associations between child abuse (experienced between ages 12-18 years) and education, psychosocial problems, symptom severity and substance abuse
Stain et al., 2014	First-episode of psychosis United Kingdom	*N*=233		BBTS	LQOLI SCFS	To investigate whether childhood adversity would be a predictor of poor social functioning in adults with psychosis

Trauelsen et al., 2016	First-episode non-affective psychosis Denmark	Patients (*n*=101), matched healthy controls (*n*=101)		CTQ-SF	PAS GAF	Studied the relationship between childhood adversity and premorbid trajectories and social outcome

Note. ASI = Addiction Severity Index; BBTS = Brief Betrayal Trauma Survey; CDRFI = Child Developmental Risk Factor Index; CTQ-SF = Childhood Trauma Questionnaire-Short Form; GAF = Global Assessment of Functioning; GBI = General Behaviour Inventory; KSADS = Schedule for Affective Disorders and Schizophrenia for School Aged Children (6-18 Years); LEQ = Life Experiences Questionnaire; LMS = Lewis–Murray Scale for Obstetric Complications; LSUR = Lifetime Substance Use Recall; LQOLI = Lehman's Quality of Life Interview; NES = Neurological Evaluation Scale; PAS = Premorbid Adjustment Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for Assessment of Positive Symptoms; SCFS = Strauss Carpenter Functioning Scale; SOFAS = Social and Occupational Functioning Assessment Scale; TEC = Trauma Experiences Checklist; TIAT = TIPP Initial Assessment Scale

CHAPTER 4
METHODOLOGY

4.1 STUDY DESIGN, SITE AND SETTING

This study is nested within two existing research projects, namely the EONKCS and Shared Roots studies. Data of study participants for this study were drawn from these two existing research projects. The principal investigator of the EONKCS study is Professor Robin Emsley. The EONKCS study was a prospective study exploring the clinical, biological and functional aspects of outcome in first-episode psychosis in South Africa. The name of the study was derived from the first letter of each of the principal investigators involved; E=Emsley; O=Oosthuizen; N=Niehaus; K=Koen; C=Chiliza and S=Schoeman. Prof Emsley granted permission to use the data of the EONKCS study for the purpose of this dissertation. Previous authors who published manuscripts from the EONKCS study data were,(Chiliza et al., 2015; Drögemöller et al., 2016; Olivier et al., 2017; Scheffler et al., 2018; Luckhoff et al., 2019).

The principal investigator of the Shared Roots study is Professor Soraya Seedat. The Shared Roots study investigated the underlying factors associated with cardiovascular risk in three patient cohorts, i.e. those with schizophrenia spectrum disorders, post-traumatic stress disorder, and Parkinson's disease. Prof Seedat granted permission to use the data of the Shared Roots study for the purpose of this dissertation. Previous authors who published manuscripts from the Shared Roots study data were, (Malan-Müller et al., 2016; O'Connell, McGregor, Emsley, Seedat & Warnich, 2019). The current cross-sectional study explored the association between premorbid adjustment and childhood trauma in first-episode schizophrenia spectrum disorders of which I am the principle investigator.

Both the larger studies recruited individuals with a first-episode of psychosis. Data collection for the larger studies took place at the Stikland Hospital Research unit, situated on the hospital grounds of Stikland Hospital in Bellville, Cape Town. The EONKCS and Shared Roots studies were both conducted by the schizophrenia research team from the Department of Psychiatry, Stellenbosch University. Data

collection for the EONKCS study commenced on the 13th of April 2007 and was completed on the 27th of February 2013. Data collection for the schizophrenia cohort of the Shared Roots study commenced on the 8th of July 2014 and was completed on the 15th of May 2018. Once the patients were recruited for both studies, they were seen by a sub-investigator (treating psychiatrist) for the consent process and screening procedures for study entry. The treating psychiatrist was also responsible for some clinical assessments as well as the treatment of the patients. A research assistant administered the cognitive assessments. I worked as a psychiatric research sister, responsible for some clinical procedures, administering of assessment scales and the overall co-ordination of both studies.

4.2 SELECTION OF STUDY PARTICIPANTS

For the two larger studies, participants were randomly recruited and entered into the studies, once they met the criteria for first-episode schizophrenia spectrum disorder. Patients were recruited from first admissions to Tygerberg and Stikland hospitals, as well as from the community health facilities in the broader Cape Town area. For the EONKCS study, the inclusion criteria were: men and women; both inpatients and outpatients; aged 16-45 years; who experienced a first psychotic episode and meeting the DSM-IV TR[1] criteria for schizophrenia or schizophreniform disorder. Exclusion criteria were: a history of any serious general medical conditions; overt current substance abuse; a lifetime exposure to antipsychotic medication for more than four weeks; and an educational level less than Grade 7. For the Shared Roots study, the inclusion/exclusion criteria were similar, except that participants younger than 18 were not included in the Shared Roots study. It is important to mention that, for the purpose of the current study, I included all participants who provided information on both premorbid adjustment as well as their childhood trauma histories. Due to the sample size, power calculations were conducted and it was found that a sample of 111 participants will provide a moderate effect size of 0.5, in keeping with the findings of Tikka et al. (2012), and will yield a power of 0.8.

[1] Diagnostic and Statistical Manual of Mental Diseases, fourth edition, text Revisions

4.3 PATIENT ASSESSMENT MEASURES

4.3.1 Socio-demographic, diagnostic, and clinical measures

The socio-demographic information collected through an interview with the patients and their primary caregivers were age, years of education, sex, and substance use. The information on substance use were obtained through urine toxicology screens for cannabis, methaqualone, and methamphetamine. A collateral history from primary caregivers on the use of substances was also collected through a clinical interview. The information on years of education was gathered from the patients together with collateral history from the primary caregivers. The patients included in both studies were able to read and write. It was required that the patients read through, complete and finally sign the consent forms.

The participants for both studies were assessed with the Structural Clinical Interview for DSM-IV (SCID), a diagnostic measure for individuals presenting with psychotic symptoms (First, Spitzer, Gibbon & Williams, 2002). Clinical information on the duration of untreated psychosis (DUP) as well as information on symptomatology were gathered. DUP refers to the period when the first psychotic symptoms manifest until the initiation of treatment with antipsychotics (Jones et al., 2005). The Positive and Negative Syndrome Scale (PANSS) were used to assess psychotic symptoms, to determine the severity of the illness. The PANSS is a 30-item scale and is administered by clinicians. The first seven items comprise the subscale for positive symptoms; items 8-14 comprise the subscale for negative symptoms, while items 15-30 comprise the subscale for symptoms of general psychopathology. The total baseline PANSS score was used as an indication of symptom severity and was calculated by adding the three subscale scores on positive, negative, and general psychopathology symptoms (Santor, Ascher-Svanum, Lindenmayer & Obenchain, 2007).

When patients became distressed at any time during assessments, they were offered to take a break. They were allowed to return for assessments on their own terms, even if we had to postpone assessments to another day. Also, patients could

withdraw from study participation at any time, without providing a reason or suffer any consequences.

4.3.2 Childhood Trauma Questionnaire, short form (CTQ-SF)

The CTQ-SF (Bernstein & Fink, 1998) is a self-report retrospective instrument that is used to measure early life trauma. Patients were asked to complete the questionnaire in the presence of a research assistant or psychiatric research sister. The questions were read to the participants and responses were written in the case report form by the research assistants. The questions were read out in the language the patients preferred, either Afrikaans or English. During completion of assessment scales, sedative medications were omitted. No retrospective instruments were completed while patients were hospitalised. The CTQ-SF has 28 Likert-type questions and provides five subscale scores, i.e. sexual abuse (i.e. “someone tried to touch me in a sexual way”), physical abuse (i.e. “people in my family hit me so hard that it left bruises or marks”), emotional abuse (i.e. “people in my family called me things like “stupid”, “lazy” or “ugly”), physical neglect (i.e. ”I didn’t have enough to eat”), and emotional neglect (i.e. “there was someone in my family who helped me feel important or special”). Subscale scores range from 5-25, and the total scale score (sum of the subscales) ranges from 25-125 (Bernstein et al., 2003). The extended 70–item CTQ has a good test–retest reliability (ICC=0.88) (Bernstein et al., 1994).

The items of the CTQ-SF hold similar meaning across diverse populations. Good evidence of criterion-related validity was also found in psychiatric ill adolescents, where collateral information was available (Bernstein et al., 2003). The validity and reliability of the CTQ-SF were found to be sound across different groups in cross-cultural settings, and has been used in South Africa. However, Spies et al., (2019) studied the psychometric properties of the CTQ-SF and found that the physical neglect subscale did not display stable factor loadings and was also not homogeneous (Spies et al., 2019). Economic and geographical factors may play a role in variations on the physical neglect subscale of the CTQ-SF across cultures (Viola et al., 2016) and needs to be revised (Spies et al., 2019). It was further advised not to exclude the physical neglect subscale but to supplement the

information on physical neglect through alternative assessments tools (see Appendices B and C for copies of the CTQ-SF instrument). The use of retrospective instruments in psychotic patient populations has received criticism. Critics argue that participants suffering from psychosis may struggle to recall on events that happened long ago, and that it may be influenced by their active psychosis. However, Fisher et al. (2011) found that psychotic individual's recollection of traumatic past experiences were not associated with current symptom severity. The Parental Bonding Instrument demonstrated high levels of concurrent validity. The convergent validity was also good with reference to the patients case notes. Patient's responses were monitored over a period of 7 years and found to be fairly stable (Fisher et al., 2011).

Kim, Bae, Han, Oh and MacDonald (2013) investigated the internal consistency and the test-retest reliability of the CTQ -SF. The outcome revealed that each type of trauma of the CTQ-SF significantly correlated with the corresponding subscales of the Trauma Antecedents Questionnaire (TAQ). The CTQ-SF further correlated with symptoms of pathological dissociation and post-traumatic stress disorder (PTSD), confirming the convergent validity of the CTQ-SF. The CTQ-SF was found to be a valid retrospective instrument to measure childhood trauma in patients with schizophrenia (Kim et al., 2013). Standard adaptation techniques, forward and back translation (i.e. from English to Afrikaans and then backward from Afrikaans to English again) were used for the translation of the CTQ-SF.

4.3.3 Premorbid Adjustment Scale

Premorbid functioning was measured using the PAS, which has good validity and inter-rater reliability, with estimates ranging between 0.74-0.85 (Cannon-Spoor et al., 1982). The PAS assessment was administered by the treating psychiatrist or the psychiatric research sister, with collateral from the primary caregivers. The PAS assesses levels of functioning in areas of sociality, peer relationships, school performance, adaptation to school, and social sexual aspects across four developmental periods. The four developmental periods included: i) childhood (up to 11 years of age); ii) early adolescence (12-15 years of age); iii) late adolescence (16-18 years of age); and iv) early adulthood (older than 19 years of age). Early adulthood was not included in the analysis, due to the effect of the early

manifestation of the illness on the adult scores (Allen et al., 2013). In childhood, social sexual aspects are not assessed. The PAS also includes a general section that assesses highest level of education, quality of life, and changes in work and school performance, which was also not included in the analysis. Item scores ranged between 0-6, with higher scores indicative of worse premorbid adjustment. The items in each subscale are normally summed and divided by the sum of the highest possible score for items completed. The total scale score is the average of the subscale scores for all subscales (Cannon-Spoor et al., 1982). The validity and reliability of the PAS are supported by a higher level of collinearity between overall adjustment and individual subscales of interest. The PAS is considered a valid instrument to assess social and academic functioning in schizophrenia (Brill, Reichenberg, Weiser & Rabinowitz, 2008). In this study, the premorbid adjustment total scale score was used, as well as two domain scores for academic and social functioning. The domain scores for academic and social functioning are distinct components of premorbid functioning (Norman, Malla, Manchanda & Townsend, 2005). Therefore, the academic and social domains of premorbid functioning were compared separately across the developmental life stages, from childhood to late adolescence. This two-factor model calculates the social premorbid adjustment domain in childhood by adding the responses to items 1 and 2, divided by the highest possible score for items completed. For the academic premorbid adjustment factor in childhood, responses for items 3 and 4 were summed and divided by the highest possible score for items completed. To calculate the early adolescent and late adolescent developmental stages (social and academic), the same procedure was applied, except for the social domain, items 1, 2 and 5 were summed and divided by the highest possible score for items completed. Item 1 measures sociability and withdrawal, item 2 measures peer relationships, item 3 measures scholastic performance, item 4 measures adaptation to school, and item 5 measures social sexual aspects. The overall PAS score was calculated based on the average of the sum of the subscale scores (social and academic domains of childhood, early adolescence and late adolescence) (Allen et al., 2013) (See Appendix D for a copy of the PAS assessment scale).

4.3.4 Life Events Checklist (LEC-5) and Life Events Timeline

The type and timing of traumatic events were assessed with the LEC-5, a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. The LEC-5 assesses exposure to 16 events known to potentially cause distress, and includes one additional item assessing any other extraordinary stressful event, not captured in the first 16 items (Weathers et al., 2013). The test-retest reliability of the LEC-5 demonstrated reasonable stability at both total scale and item level scores, in both non-clinical and clinical samples (r=.34-.48) and was found to be similarly correlated with PTSD symptom severity. The LEC-5 is used as a screening tool to measure exposure to direct potentially traumatic events, in other words to investigate the consistency for the events experienced by an individual (Gray, Litz, Hsu & Lombardo, 2004). Standard adaptation techniques were also used for the translation of the LEC-5 from English to Afrikaans. The patients also completed a Life Events Timeline in the presence of the researcher that captured traumatic life events at certain ages, over the participant's lifespan. The LEC-5 and Life Events Timeline were used to ensure that histories of childhood trauma did not go unnoticed. These were further used to elaborate on the timing of childhood trauma experienced. Childhood trauma experienced beyond the five childhood trauma subscales of the CTQ-SF was not analysed in this study (see Appendices E and F for copies of the LEC-5 instruments and Appendix G for a copy of the Life Events Timeline).

4.4 DATA MANAGEMENT

The clinical and demographic data of the EONKCS study was gathered and recorded in the clinical source notes of the participants. The assessment scales were captured on a hard copy of a case report form (CRF). Thereafter, the data was captured onto an electronic database by the researcher. Following electronic data capturing, the data entries were cross-checked by a second research assistant, together with quality control of the data. The same procedures applied for the Shared Roots study, except for the electronic data capturing. The data of the Shared Roots study was captured onto a secure platform, Research Electronic Data Capture (REDCap) by a research assistant, as well as the researcher. REDCapTM is a web-

based tool for data capturing, developed at Vanderbilt University in Nashville, USA. It is a sophisticated platform that offers many tools that can be tailored for any research design. REDCap also allows the upload of documents on the platform. The data can be exported from REDCap to Excel and different statistical packages for analysis (Klipin, Mare, Hazelhurst & Kramer, 2014).The data entries in REDCap were also crosschecked by a second research assistant, together with quality control of the data.

4.5 DATA ANALYSIS

The Statistical Package for Social Sciences (SPSS), IBM software, statistics 25 was used for statistical analyses, performed by the researcher and checked by the supervisors of the study. Descriptive statistics were used to describe patient's demographic and clinical information. Within the patient group, Pearson correlation coefficients were calculated in order to assess the linear relationship between childhood trauma exposure and premorbid adjustment measures. Hierarchical linear regression analysis was used to further explore the effects of childhood trauma and premorbid adjustment. Relevant socio-demographic and clinical predictors of interest were done to study the relationship between childhood trauma and premorbid adjustment based on significant associations evident from preliminary correlation testing. This type of regression allows one to determine whether the main variables of interest explain a significant proportion of variance in the dependent variable, independent of other known significant variables (Field, 2009).

The following steps were followed during the hierarchical regression analysis. To study the relationship between demographic variables and premorbid functioning in childhood, education was entered into the model first, followed by the childhood trauma variables physical abuse and physical neglect. To study the relationship between clinical and demographic variables and premorbid functioning during early adolescence, education and PANSS total scores were entered first, followed by the childhood trauma variables physical and sexual abuse, as well as physical neglect, and CTQ total scores. The interaction between global childhood trauma exposure (CTQ total scores) and timing of trauma was also explored. To study associations between overall premorbid functioning, education and PANSS total baseline score

were first entered, followed by the childhood trauma variables physical abuse and physical neglect.

Post-hoc correlation analyses were used to more comprehensively describe the relationships between childhood trauma exposure and specific domains of social and academic premorbid functioning, again in relation to relevant socio-demographic and clinical variables of interest. The post-hoc hierarchical regression were done, informed by the relationships that stood out in the post-hoc correlation analysis. Concerning academic functioning in childhood, education was entered into the model first, and thereafter the childhood trauma variables, physical abuse and neglect. To study the next outcome variable, premorbid academic functioning in early adolescence, demographic variables, education and the variable substance use were entered in the model first. Then the childhood trauma variables physical neglect and overall childhood trauma were entered. To further study significant associations with social functioning in early adolescence, DUP was entered into the model first followed by entering physical neglect. To study the variables of interest concerning social functioning in late adolescence, age at study entry was entered into the model first, thereafter the childhood trauma variables physical abuse and neglect, sexual abuse, and overall childhood trauma were entered. We were also interested in the interaction between trauma timing and type and premorbid adjustment in the total patient sample.

4.6 CONFIDENTIALITY AND ETHICAL CONSIDERATIONS

The studies from which the data was utilised for this study were approved by the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University. (EONKCS study, ethics clearance reference number: N06/08/148), (see Appendix H for a copy of the ethical clearance and Appendix I for a copy of the approval from the Department of Health for the EONKCS study). (Shared Roots study, ethics clearance reference number: N13/08/115), (see Appendix J for a copy of the ethics clearance and Appendix K for a copy of the approval from the Department of Health for the Shared Roots study). Extension/annual renewal of ethics approval for both studies were approved by The Health Research Ethics Committee, Stellenbosch University for 2019. The Health

Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University also approved the sub-study; The association between premorbid adjustment and childhood adversity in first-episode schizophrenia (Ethics clearance reference number: S19/05/098) (see Appendix L for a copy of the ethical clearance for the sub-study). An application for an amendment on the study title were requested and The Health Research Ethics Committee of Stellenbosch University approved the amendment: The association between premorbid adjustment and childhood trauma in first-episode schizophrenia spectrum disorders (Ethics clearance reference number: S19/05/098) (See Appendix M for a copy of the approval of the amendment).

All the procedures related to the studies complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The research team involved in the EONKCS and Shared Roots studies received training on the study protocols and study procedures. Inter-rater reliability training of the assessments scales as well as training on Good Clinical Practise (GCP) were required from all members of the research team. GCP is an international scientific and ethical standard for the design, conduct, analysis, and reporting of clinical data. It further insures accurate and credible research, to respect the rights, confidentiality and integrity of study participants. The Declaration of Helsinki 1975 stipulates the ethical principles, underlying the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-GCP guidelines (Vijayananthan & Nawawi, 2008).

Written informed consent was obtained from all participants and in the case of minors, assent was obtained from the participants, including consent from the parent or legal guardian. Prior to the consent process, the participants were given ample time to decide on participation in the study. All questions, concerns, and possible risks concerning the study were addressed during the consent process. The participants were also informed that they have the right to withdraw from the study at any time, that they can withdraw without providing an explanation and will not suffer any consequences, should they decide on early termination of the study. As for the patients, prior to the consent process, alternative options for treatment of the illness

were offered. The patients were also informed that in the opinion of the clinician in terms of the efficacy and side-effect profile to antipsychotic treatment, they might have to terminate study participation. In such a case, the patients were referred to other psychiatric services for alternative treatment and follow-up.

The participants were assured that all study information would be treated as confidential. The collected data were stored under a participant identification code allocated to them in order to protect their identity. The participants were also informed that only members of the research team will have access to their data and that their personal information will not be revealed in any database, research paper, or research article. The identification codes were linked to their full names and surnames. The personal information of the participants were filed in an investigator file, together with the original signed consent forms and stored in a secure location at the Stikland Hospital Research unit, with no unauthorized access. The electronic databases of both studies allow access through usernames and passwords only, for protection against unauthorized access (see Appendices N and O for copies of consent forms).

CHAPTER 5
RESULTS AND DISCUSSION

5.1 RESULTS

The total sample consisted of 111 first-episode schizophrenia spectrum disorder patients, seventy-seven of whom were male (69%). Mean age at study entry was 24.9 years (SD=6.9). Patients had a mean highest level of education of 10 years (SD=2.1). Seventy-six patients were diagnosed with schizophrenia, 34 with schizophreniform disorder, and one with schizoaffective disorder. Patients had a mean duration of untreated psychosis (DUP) of 41.8 weeks (SD=60.8) and a mean baseline Positive and Negative Syndrome Scale (PANSS) total score of 93.2 (SD=17.2). In total, 54 patients (49%) reported that they have used substances prior to study entry.

5.1.1 Childhood trauma exposure and premorbid developmental periods

Patients experienced high levels of the following childhood trauma types: 41 (39%) were exposed to high levels of emotional abuse, 34 (32%) to high levels of physical abuse, 26 (24%) to high levels of sexual abuse, 38 (36%) to high levels of physical neglect and 26 (26%) to high levels of emotional neglect. Fifty-two patients (56%) fell into the high overall childhood trauma category. Only a subset of the patients (*n*=53) provided information on timing of childhood trauma. Thirty-four patients (64%) reported trauma exposure <12 years of age and 19 (36%) reported trauma ≥12 years of age. Additional information regarding childhood trauma exposure is provided in Table 2 below and Appendix R.

Detailed information for individual items measured during each premorbid developmental period is also presented in Table 2 below. During childhood, patients had a median premorbid functioning score of 0.33 [0–1.50]; a median score of 0.58 [0-1.28] during early adolescence, a median score of 0.67 [0-1.69] in late adolescence, and a median overall premorbid adjustment score of 0.28 [0-0.66].

Table 2. Childhood trauma exposure and premorbid adjustment scores (PAS) in three developmental periods

Patients only

CT Age, mean (SD)	9.31 (3.85)
CTQ-EA Total (*n*=107), median (range)	11.00 [5-24]
CTQ-PA Total (*n*=103), median (range)	7.00 [5-24]
CTQ-SA Total (*n*=107), median (range)	5.00 [5-25]
CTQ-EN Total (*n*=101), median (range)	9.00 [5-23]
CTQ-PN Total (*n*=102), median (range)	9.00 [5-22]
CTQ-Overall (*n*=96), median (range)	44.00 [25-92]

Developmental Period	**PAS scores median (range)**
Childhood (up to 11 years)	
Sociability and withdrawal (n=111)	0.00 [0-6]
Peer relationships (n=111)	1.00 [0-6]
Scholastic performance (n=111)	3.00 [0-6]
Adaption to school (n=111)	0.00 [0-6]
Early adolescence (12 - 15 years)	
Sociability and withdrawal (n=111)	0.00 [0-6]
Peer relationships (n=111)	2.00 [0-6]
Scholastic performance (n=108)	3.00 [0-6]
Adaption to school (n=108)	0.50 [0-5]
Socio-sexual aspects of life (n=111)	1.00 [0-6]
Late adolescence (16 - 18 years)	
Sociability and withdrawal (n=110)	1.00 [0-6]
Peer relationships (n=110)	2.00 [0-5]
Scholastic performance (n=96)	4.00 [0-6]
Adaption to school (n=98)	2.00 [0-6]
Socio-sexual aspects of life (n=110)	2.00 [0-6]

CT = Childhood Trauma; CTQ= Childhood Trauma Questionnaire; EA = Emotional Abuse; EN = Emotional Neglect; PA = Physical Abuse; PAS = Premorbid Adjustment Score; PN = Physical Neglect

5.1.2 Correlations between childhood trauma, clinical information, demographics and premorbid adjustment

The correlation results are presented in Table 3. In summary (see also Supplementary Figure 2 in Appendix P), education was the only demographic variable that correlated significantly with premorbid adjustment. There was a negative correlation between education and premorbid functioning overall scores, as well as for the childhood and early adolescence domain scores. Lower education was associated with worse premorbid adjustment. In terms of clinical variables, worse overall psychopathology severity (i.e. higher PANSS total score) was associated with worse premorbid functioning overall and during early adolescence. The following childhood trauma sub-types were positively associated with worse premorbid adjustment: physical and sexual abuse, as well as physical neglect. Higher physical abuse correlated with worse premorbid functioning during childhood and early adolescence, while higher sexual abuse correlated with worse premorbid functioning in early adolescence. Higher physical neglect correlated with worse premorbid functioning overall as well as during childhood and early adolescence. Higher total childhood trauma correlated with worse premorbid functioning during early adolescence.

Table 3. Pearson correlations between childhood trauma and developmental stages of premorbid adjustment

	PAS Childhood Total		PAS Early Adolescence Total		PAS Late Adolescence Total		PAS Overall Total	
	rho value	*p* value	rho value	*p* value	rho value	*p* value	rho value	*p* value
Age at study entry in years	.07	.46 (*n*=112)	-.09	.34 (*n*=112)	-.16	.10 (*n*=111)	-.09	.37 (*n*=112)
Sex	-.11	.24 (*n*=112)	-.09	.34 (*n*=112)	-.07	.48 (*n*=111)	-.11	.26 (*n*=112)
Education in years	-.26*	<.05 (*n*=88)	-.37**	<.01 (*n*=88)	-.18	.11 (*n*=87)	-.31**	<.01 (*n*=88)
PANSS Total	.09	.32 (*n*=112)	.22*	<.05 (*n*=112)	.15	.11 (n=111)	.19*	<.05 (*n*=112)
DUP	-.02	.82 (*n*=110)	-.09	.37 (*n*=110)	-.08	.43 (*n*=109)	-.08	.39 (*n*=110)
CTQ-EA	.11	.25 (*n*=104)	.13	.20 (*n*=104)	-.10	.30 (*n*=103)	.04	.66 (*n*=104)
CTQ-PA	.21*	<.05 (*n*=106)	.22*	<.05 (*n*=106)	.07	.50 (*n*=105)	.20*	<.05 (*n*=106)
CTQ-SA	.19	.05 (*n*=108)	.20*	<.05 (*n*=108)	.08	.44 (*n*=107)	.19	.05 (*n*=108)
CTQ-PN	.31**	<.01 (*n*=105)	.35**	<.01 (*n*=105)	.05	.63 (*n*=104)	.27**	<.01 (*n*=105)

CTQ-EN	.02	.81 (*n*=102)	.07	.52 (*n*=102)	.12	.22 (*n*=101)	.09	.36 (*n*=102)
CTQ-Total	.18	.08 (*n*=93)	.23*	<.05 (*n*=93)	.06	.57 (*n*=92)	.18	.08 (*n*=93)
CT Age continuous	-.10	.49 (*n*=54)	.13	.37 (*n*=54)	-.04	.80 (*n*=54)	-.10	.45 (*n*=54)

Note.*p≤.05; **p≤.01; CT = Childhood Trauma; CTQ = Childhood Trauma Questionnaire; DUP = Duration of untreated psychosis; EA = Emotional Abuse Subscale; EN = Emotional Neglect Subscale; PA = Physical Abuse Subscale; PANSS = Positive and Negative Syndrome Scale; PN = Physical Neglect Subscale; PAS = Premorbid Adjustment Scale; SA = Sexual Abuse Subscale

5.1.3 Results of the hierarchical regression analysis

Informed by the significant associations described above, regression analyses were subsequently performed. Individual hierarchical regressions were run for three of the four outcome measures (PAS childhood, PAS early adolescence, and PAS overall) (see Table 4 below).

To study the relationship between demographic variables and premorbid functioning in childhood, education was entered in model I, adjusting for the childhood trauma variables physical abuse and physical neglect in model II. None of the variables included in the model demonstrated a significant relationship with premorbid functioning during childhood. Then, to study the relationship between clinical and demographic variables and premorbid functioning during early adolescence, education and PANSS total baseline score were first entered in model I, adjusting for the childhood trauma variables in model II, which included: physical and sexual abuse, physical neglect, childhood trauma total, as well as the interaction between timing of childhood trauma and childhood trauma total scale score. The only significant association detected was between physical neglect and premorbid functioning during early adolescence. To study associations between overall premorbid functioning, education and PANSS total baseline score were first entered in model I, adjusting for childhood trauma variables physical abuse and neglect in model II. However, none of the variables explained a significant proportion of variance in overall premorbid functioning.

Table 4. Hierarchical regression of childhood trauma variables and the developmental stages of premorbid adjustment

Overall PAS Childhood (*n*=104)							
Model					Predictor		
	R^2	df	F	p Values	β	t	p Values
Model I	.06	1	5.08	<.05			
Education years					-.25	-2.26	<.05
Model II	.07	3	1.93	.13			
Education years					-.22	-1.90	.07
CTQ-PA					.04	.32	.75
CTQ-PN					.08	.66	.51

Overall PAS Early Adolescence (*n*=104)							
Model					Predictor		
	R^2	df	F	p Values	β	t	p Values
Model I	.15	2	4.76	<.05			
Education years					-.31	-2.35	.05
PANSS Total					.15	1.19	.24
Model II	.22	7	2.27	<.05			

Education years					-.23	-1.71	.09
PANSS Total					.18	1.35	.19
CTQ-PA					.25	1.22	.23
CTQ-SA					.13	.69	.50
CTQ-PN					.45	2.16	<.05
CTQ-Total					-.67	-1.88	.07
Timing CT*CTQ Total					.18	1.10	.28
Overall PAS Total (*n*=104)							
Model					Predictor		
	R^2	df	F	p Values	β	t	p Values
Model I	.11	2	4.83	<.05			
Education years					-.23	-1.98	.05
PANSS Total					.17	1.47	.15
Model II	.12	4	2.61	<.05			
Education years					-.19	-1.54	.13
PANSS-Total					.18	1.55	.13
CTQ-PA					.04	.34	.74
CTQ-PN					.09	.73	.47

Note. CT Age CAT = Childhood Trauma as a categorical variable, early or later age; CTQ = Childhood Trauma Questionnaire; PA = Physical Abuse; PANSS = Positive and Negative Syndrome Scale; PAS = Premorbid Adjustment Scale; PN = Physical neglect; SA = Sexual Abuse

5.1.4 Physical neglect and premorbid functioning in early adolescence: A post-hoc analysis

Given the significant relationship between physical neglect and premorbid functioning during early adolescence, a post-hoc analysis was conducted in order to disentangle this association. More specifically, this was done to explore the effect of physical neglect on specific premorbid factors during early adolescence. It is possible to calculate separate scores for social and academic functioning during each premorbid developmental period. In addition, the relationship between childhood trauma and academic and social functioning during the other two developmental periods (i.e. childhood and late adolescence) were also explored as part of the post-hoc analysis. This was done to confirm that no significant relationships went undetected by focusing primarily on total premorbid adjustment during each developmental period.

The post-hoc analysis included two steps (see Supplementary Figure 3 in Appendix Q). As a first step, a bivariate correlation analysis was performed to explore relationships between clinical, demographic and childhood trauma variables and premorbid social and academic functioning during childhood and adolescence (early and late). Informed by the significant associations found in the correlation analysis, a post-hoc regression analysis was done. Individual hierarchical regressions were performed for four of the six outcome measures.

5.1.5 Results of the post-hoc correlation analysis

Results of the correlation analysis (Table 5) revealed that age at study entry and years of education were significantly correlated with premorbid functioning. Age at study entry had a negative correlation with social and academic functioning in late adolescence. A lower age was associated with worse social and academic premorbid functioning. Years of education had a negative correlation with academic functioning in childhood, early adolescence and late adolescence. Less years of education were associated with poorer academic premorbid adjustment. Worse symptom severity (i.e. higher PANSS total baseline score) was associated with poorer late adolescent academic functioning. DUP demonstrated a significant

inverse correlation with social functioning in early adolescence. A shorter DUP was associated with poorer premorbid social functioning in early adolescence. The childhood trauma sub-types that correlated with premorbid academic and social functioning included physical abuse and physical neglect, as well as sexual abuse. Physical abuse was significantly associated with worse premorbid academic functioning in childhood and worse premorbid social functioning during late adolescence. Physical neglect was significantly associated with poorer academic premorbid functioning in childhood and early adolescence. Physical neglect was also significantly associated with worse social premorbid functioning in early and late adolescence. Sexual abuse significantly correlated with poorer social functioning in late adolescence. Higher overall childhood trauma was significantly correlated with worse social premorbid adjustment in late adolescence as well as worse academic premorbid functioning in early adolescence. In addition, an ANOVA was performed to study the associations of substance use with premorbid social and academic functioning. Academic functioning during both late adolescence and early adolescence were poorer among substance users compared to their non-using counterparts (See Appendix S for details of the ANOVA).

5.1.6 Results of the post-hoc regression analysis

Informed by the significant associations found in the correlation analysis a post-hoc regression analysis was done. Individual hierarchical regression models were performed for four of the six outcome measures (PAS childhood academic, PAS early adolescent academic and social, including PAS late adolescent social) (see Table 6 below).

To further investigate the relationships that stood out in the correlation analysis, concerning academic functioning in childhood, education was entered into the model I first. Thereafter, it was adjusted for the childhood trauma variables, physical abuse and neglect in model II. Education demonstrated a significant relationship with childhood academic functioning. To study the next outcome variable, premorbid academic functioning in early adolescence, demographic variables, education and substance use were entered in model I. Thereafter, it was adjusted for the childhood trauma variables physical neglect and overall childhood

trauma in model II. None of the childhood trauma variables demonstrated a significant relationship, however years of education displayed a significant relationship with academic functioning in early adolescence. To further study significant associations with social functioning in early adolescence, DUP was entered into the model I and adjusted for physical neglect in model II. Both DUP and physical neglect had a significant relationship with premorbid social functioning in early adolescence. To study the variables of interest concerning social functioning in late adolescence, age at study entry was entered into the model I, adjusting for the childhood trauma variables physical abuse and neglect, sexual abuse, and overall childhood trauma in model II. Age at study entry was the only variable with a significant relevance to social functioning in late adolescence.

Table 5. Pearson correlations between childhood trauma and the social and academic domains of premorbid adjustment across all developmental stages

		PAS Childhood Academic		PAS Childhood Social		PAS Early Adolescence Academic		PAS Early Adolescence Social		PAS Late Adolescence Academic		PAS Late Adolescence Social
	rho value	*p* value	rho value	*p* value	rho value	*p* value	rho value	*p* value	rho value	*p* value	rho value	*p* value
Age at study entry in years	.09	.37 (*n*=111)	-.08	.40 (*n*=111)	-.03	.78 (*n*=108)	-.09	.37 (*n*=111)	-.22*	<.05 (*n*=98)	-.25**	<.01 (*n*=111)
Gender	-.13	.19 (*n*=111)	-.06	.51 (*n*=111)	-.18	.06 (*n*=108)	-.01	.95 (*n*=111)	-.13	.20 (*n*=98)	-.06	.52 (*n*=111)
Education in years	-.39**	<.01 (*n*=87)	.02	.84 (*n*=87)	-.59**	<.01 (*n*=86)	-.05	.64 (*n*=87)	-.57**	<.01 (*n*=76)	-.17	.11 (*n*=87)
PANSS Total	.18	.06 (*n*=111)	.08	.43 (*n*=111)	.17	.09 (*n*=108)	.17	.07 (*n*=111)	.22*	<.05 (*n*=98)	.19	.05 (*n*=111)
DUP	.14	.14 (*n*=109)	-.06	.53 (*n*=109)	.19	.05 (*n*=106)	-.24*	<.05 (*n*=109)	.12	.24 (*n*=96)	-.14	.16 (*n*=109)
CTQ-EA	.15	.13 (*n*=103)	-.00	.98 (*n*=103)	.18	.08 (*n*=100)	.02	.81 (*n*=103)	.01	.94 (*n*=90)	.13	.20 (*n*=103)

CTQ-PA	.21*	<.05 (*n*=105)	.12	.21 (*n*=105)	.13	.19 (*n*=102)	.19	.06 (*n*=105)	.13	.22 (*n*=92)	.25*	<.05 (*n*=105)
CTQ-SA	.18	.06 (*n*=107)	.03	.79 (*n*=107)	.11	.26 (*n*=104)	.17	.09 (*n*=107)	.11	.29 (*n*=94)	.23*	<.05 (*n*=107)
CTQ-PN	.29**	<.01 (*n*=104)	-.13	.18 (*n*=104)	.28**	<.01 (*n*=101)	.25*	<.05 (*n*=104)	.18	.08 (*n*=93)	.20*	<.05 (*n*=104)
CTQ-EN	.06	.57 (*n*=101)	.08	.42 (*n*=101)	.09	.40 (*n*=99)	-.00	.99 (*n*=101)	.03	.80 (*n*=90)	.07	.48 (*n*=101)
CTQ-Total	.19	.08 (*n*=92)	.09	.37 (*n*=92)	.21*	<.05 (*n*=90)	.13	.21 (*n*=92)	.09	.41 (*n*=82)	.23*	<.05 (*n*=92)
Age timing continuous	-.06	.69 (*n*=53)	-.08	.56 (*n*=53)	-.12	.42 (*n*=50)	-.08	.60 (*n*=53)	-.13	.37 (*n*=47)	-.17	.23 (*n*=53)

Note. *p≤.05; **p≤.01; CT = Childhood Trauma; CTQ = Childhood Trauma Questionnaire; DUP = Duration of untreated psychosis; EA = Emotional Abuse Subscale; EN = Emotional Neglect Subscale; PA = Physical Abuse Subscale; PANSS = Positive and Negative Syndrome Scale; PN = Physical Neglect Subscale; PAS = Premorbid Adjustment Scale; SA = Sexual Abuse Subscale

Table 6. Hierarchical regression of childhood trauma variables and the social and academic domains of premorbid adjustment

Overall PAS Childhood Academic (n=111)							
Model					Predictor		
	R^2	df	F	p	β	t	p Values
Model I	0.14	1	12.63	0.001			
Education years					-0.38	-3.55	0.001
Model II	0.15	3	4.31	0.007			
Education years					-0.35	-3.10	0.003
CTQ-PA					0.06	0.50	0.619
CTQ-PN					0.04	0.34	0.733
Overall PAS Early Adolescence Academic (n=108)							
Model					Predictor		
	R^2	df	F	p	β	t	p Values
Model I	0.34	2	18.84	0.000			
Education years					-0.59	-5.75	0.000
Substance use					-0.02	- 0.16	0.873
Model II	0.34	4	9.17	0.000			
Education years					-0.60	-5.44	0.000
Substance use					-0.02	- 0.16	0.872
CTQ-PN					-0.02	- 0.12	0.906

CTQ-Total					0.00	0.03	0.977
Overall PAS Early Adolescence Social (n=111)							
Model					Predictor		
	R^2	df	F	p Values	β	t	p Values
Model I	0.06	1	6.42	0.013			
DUP					-0.25	-2.53	0.013
Model II	0.13	2	7.08	0.001			
DUP					-0.23	-2.44	0.017
CTQ-PN					0.26	2.71	0.008
Overall PAS Late Adolescence Social (n=111)							
Model					Predictor		
	R^2	df	F	p Values	β	t	p Values
Model I	0.05	1	4.82	0.031			
Age at study entry					-0.23	-2.20	0.031
Model II	0.15	5	3.01	0.015			
Age at study entry					-0.21	-2.09	0.040
CTQ-PA					0.29	1.67	0.099
CTQ-PN					0.30	1.87	0.065
CTQ-SA					0.16	1.21	0.231
CTQ-Total					-0.32	-1.18	0.240

Note. CTQ = Childhood Trauma Questionnaire; PA = Physical Abuse; PANSS = Positive and Negative Syndrome Scale; PAS = Premorbid Adjustment Scale; PN = Physical Neglect; SA = Sexual Abuse

5.2 DISCUSSION

In contrast to our initial hypotheses, global childhood trauma exposure was not significantly associated with overall premorbid adjustment in first-episode schizophrenia spectrum disorder patients. In addition, timing of exposure did not emerge as a significant moderator of the relationships between childhood trauma and premorbid functioning. However, we demonstrated a significant association between physical neglect and poorer premorbid adjustment during early adolescence. In addition, post-hoc analyses revealed a significant relationship between physical neglect and premorbid social functioning during early adolescence. Important individual associations of age, DUP and years of education with specific domains of premorbid functioning were also evident.

In keeping with our previous work conducted in a similar first-episode sample (Kilian et al., 2017), the present findings suggest a detrimental association of physical neglect with poorer premorbid social functioning during early adolescence. In comparison, research conducted in chronic schizophrenia suggest an association of premorbid social functioning with emotional rather than physical neglect (Chan et al., 2018). The association between physical neglect and premorbid adjustment evident from our study is not surprising, given the poor socio-economic circumstances of our participants. The study catchment area is characterised by extreme poverty and high unemployment rates. The CTQ physical neglect subscale taps into poverty, and includes items asking patients to report if they had enough to eat while growing up. They were also asked whether they had proper shelter, a secure environment, and access to proper medical care while growing up. Unmet physical needs have a major impact on adult social functioning in schizophrenia (Gil et al., 2009). Physical neglect experienced during childhood may have lasting effects, which eventually affects social functioning in adulthood (Weaver et al., 2004). Children exposed to persistent physical neglect often suffer social difficulties during childhood, and these social problems are carried into early adolescence (Bornstein, Hahn & Haynes, 2010). Early adolescence is associated with the start of neuro-endocrinological changes including an increased sensitivity to stress. Stress associated with physical neglect during this sensitive period of neurodevelopment may result in abnormal behavioural

development (Romeo, 2013), increasing the risk of social withdraw and avoidant peer interactions (Hildyard & Wolfe, 2002). Adolescents exposed to physical neglect often lack proper social skills (Manly, Kim, Rogosch & Cicchetti, 2001) and suffer more severe emotional problems, e.g. an increased risk of social isolation (Hildyard & Wolfe, 2002).

DUP was also associated with poorer social functioning during early adolescence in our sample. Barnes et al. (2008) found that a longer DUP was an independent predictor of overall social functioning in patients with schizophrenia. Haahr et al. (2016) reported a significant association between poorer premorbid adjustment in late adolescence and childhood trauma before the age of 18. It was argued that the reason for delayed help seeking behaviour, which is known to be associated with a longer DUP (Tait, 2004; Berry et al., 2007), could be attributed to a lack of trust of other people as a consequence of exposure to childhood trauma (Haahr et al., 2016). Jeppesen et al. (2008) found that a longer DUP is independently associated with positive symptoms, while poor premorbid social functioning was independently associated with negative symptoms and a smaller social network (Jeppesen et al., 2008). Social competence and good social skills may serve as protective factors in patients with schizophrenia, compensating for better cognitive function, neurobiological vulnerability, social adjustment, and the effects of stressful events. Good social skills and social competence may increase resilience (Salokangas, Honkonen, Stengard & Koivisto, 2006), allow for better problem solving skills to daily life hassles, improve adherence to treatment (Liberman & Kopelowicz, 2005), prevent exacerbations (Kopelowicz, Liberman, & Zarate, 2006), and improve quality of life (Salokangas et al., 2006). Adolescents with poor social skills tend to socially withdraw from their peers, endure parental over protectiveness with poor reciprocal responses from the environment, and therefore no positive reinforcement for social skill development (Nisenson & Berenbaum, 1998). Our findings suggest individuals with poor social functioning during early adolescence are more likely to have a shorter DUP. In line with findings reported by Drake, Haley, Akhtar and Lewis (2000), one possible explanation for this finding is that more maladjusted patients suffer higher levels of pre-occupation or hostility, including poorer coping skills, in part due to a history of substance use, resulting in earlier help seeking behaviour.

Burns (2012) found that the use of cannabis shortly before the patients reached out for help resulted in disruptive behaviour, forcing the family members of the patients to seek help earlier.

Mental health service accessibility is an important factor to consider when studying the duration of untreated psychosis. Although psychiatric services in the Cape Town area have improved through the establishment of outreach psychiatric facilities (Hering, Koen, Joska, Botha & Oosthuizen, 2008), there are still many South Africans who are unable to easily access mental health services due to various factors, such as language barriers (Stolk et al., 1998) and the affordability of transport among the poor (Bruwer et al., 2011).

The demographic variables with significant relevance to premorbid functioning included years of education and age at study entry. Education demonstrated a significant relationship with premorbid academic functioning in early adolescence. This finding is consistent with those reported by Larsen et al. (2004), who found an association between poorer premorbid academic achievement and lower levels of education. Education is the foundation of academic performance, and it is therefore not surprising that it was associated with premorbid academic performance. For example, education enhances the development of the brain's language systems, improving language-based semantic memory over time (Nyberg et al., 2003). In a subgroup of patients with schizophrenia, years of education may serve as a protective factor. It has been reported that higher levels of education as well as complex occupations are associated with less cognitive impairment and better outcomes (Robertson, 2014). Patients with higher levels of education suffer less psychotic symptomatology, and reported better premorbid social functioning and academic performance. Education was found to be an important predictor of premorbid functioning in schizophrenia (Swanson, Gur, Bilker, Petty & Gur, 1998).

Age at study entry further demonstrated a significant relevance to poorer social functioning in late adolescence in the present study. This finding suggests that an earlier age of illness onset could be as a consequence of substance use, in particular cannabis use, reported among the majority (69%) of male patients in our sample. This finding supports those reported by Myles, Newall, Nielssen and Large

(2012), who identified cannabis use as an independent predictor of an earlier age of disease onset in a sample of male patients with schizophrenia spectrum disorder, regardless of whether they smoked tobacco or not.

In summary, we replicated a significant association between physical neglect and poorer premorbid functioning during early adolescence in first-episode schizophrenia spectrum disorder patients. In addition, significant associations of premorbid adjustment with age at study entry, DUP, and education level were evident.

CHAPTER 6
LIMITATIONS, STRENGHTS, RECOMMENDATIONS, AND FINAL CONCLUSION

6.1 STUDY LIMITATIONS AND STRENGTHS

Limitations of the study included the following. Firstly, the sample size was small, and a larger sample size could have provided additional power to study the effect of timing on the relationship between childhood trauma and premorbid adjustment. Secondly, the cross-sectional nature of the study design does not allow for inferences on causality to be made (Reichenheim & Coutinho, 2010). Thirdly, use of a retrospective assessment scale to gather data on childhood trauma was an important limitation, which can result in recall bias and unreliability. A research assistant helped patients complete all study questionnaires, to make sure the questions were understood. A study conducted to investigate the validity of retrospective reports on childhood trauma reported that the errors of measurement do not have a significant effect on study validity (Fergusson, Horwood & Borden, 2011). However, Spies et al. (2019) recommended that researchers supplement their enquiry on the physical neglect subscale of the CTQ-SF with other assessment measures, due to the poor internal consistency of physical neglect, found in a recent study.

However, our study also had important strengths which should be acknowledged. For example, supplementary assessment measures (LEC-5 and Life Events Timeline) were used to make sure the information on the childhood trauma subscales were thorough and accurate. Childhood trauma subtypes and their specific effects on premorbid functioning were assessed. The study included a comprehensive assessment of social and academic domains and developmental periods of premorbid adjustment, which allows for a rich understanding of the extent to which premorbid adjustment is affected. The study findings contribute to the small body of research conducted on the subject matter in first-episode samples. We furthermore controlled for multiple confounding factors through the use of a

hierarchical regression. Lastly, the study highlights the effects of childhood trauma on psychotic spectrum disorders in a developing country.

6.2 FUTURE RECOMMENDATIONS

Future longitudinal studies should be conducted in larger samples. It would be important to obtain information about the long-term consequences of poor premorbid functioning due to childhood trauma. For example, it would have clinical value to study whether poor premorbid social functioning due to a history of childhood trauma is associated with poor social functioning and social cognition in FES patients. This is important, given that physical neglect is linked to chronic stress with altered amygdala and cortical brain volumes (LoPilato et al., 2018), a known risk factor for emotional dysregulation (Jin, 2014) linked to poorer social cognition in schizophrenia (Rowland et al., 2013). To the best of my knowledge, only one study (Alameda et al. 2015) previously assessed the specific timing of childhood trauma and its associations with premorbid functioning. More research is needed to determine whether timing is indeed playing a moderating role in the relationship between childhood trauma and premorbid social and academic functioning. Future studies should include matched controls as this could help to identify illness specific effects on premorbid adjustment, to disentangle which effects are due to the illness and not due to a history of childhood trauma. It would also be important for future studies to look at the interaction effect of DUP, years of education and age at study entry when studying the relationship between childhood trauma and premorbid adjustment.

6.3 GENERAL RESEARCH CONCLUSION

The study suggests that there could be a link between physical neglect and premorbid adjustment. The findings suggest that physical neglect is associated with poorer social functioning during the ages of 12-15 years/early adolescence, which is a sensitive developmental period. This finding however does not imply a causal relationship, because this study did not control for family support and resilience nor did it include a matched control group. Social impairments that occur during early adolescence could place individuals at greater risk to develop schizophrenia (Tarbox et al., 2012). The effects of childhood trauma on premorbid social and academic

functioning may persist into adulthood and lead to poorer clinical and cognitive outcomes in patients living with schizophrenia (Perez & Widom, 1994; Weaver et al., 2004; Lecomte et al., 2008; Bornstein et al., 2010). Given that schizophrenia contributes significantly to the global burden of disease (Bhugra, 2005), it is crucial to address the impact of neglect on mental health in a country such as South Africa, which is characterized by high levels of social inequality and poverty. Mental health professionals working in South Africa should invest in routine screenings of childhood neglect to assure the implementation of early preventative measures.

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APPENDICES

APPENDIX A: Supplementary Figure 1

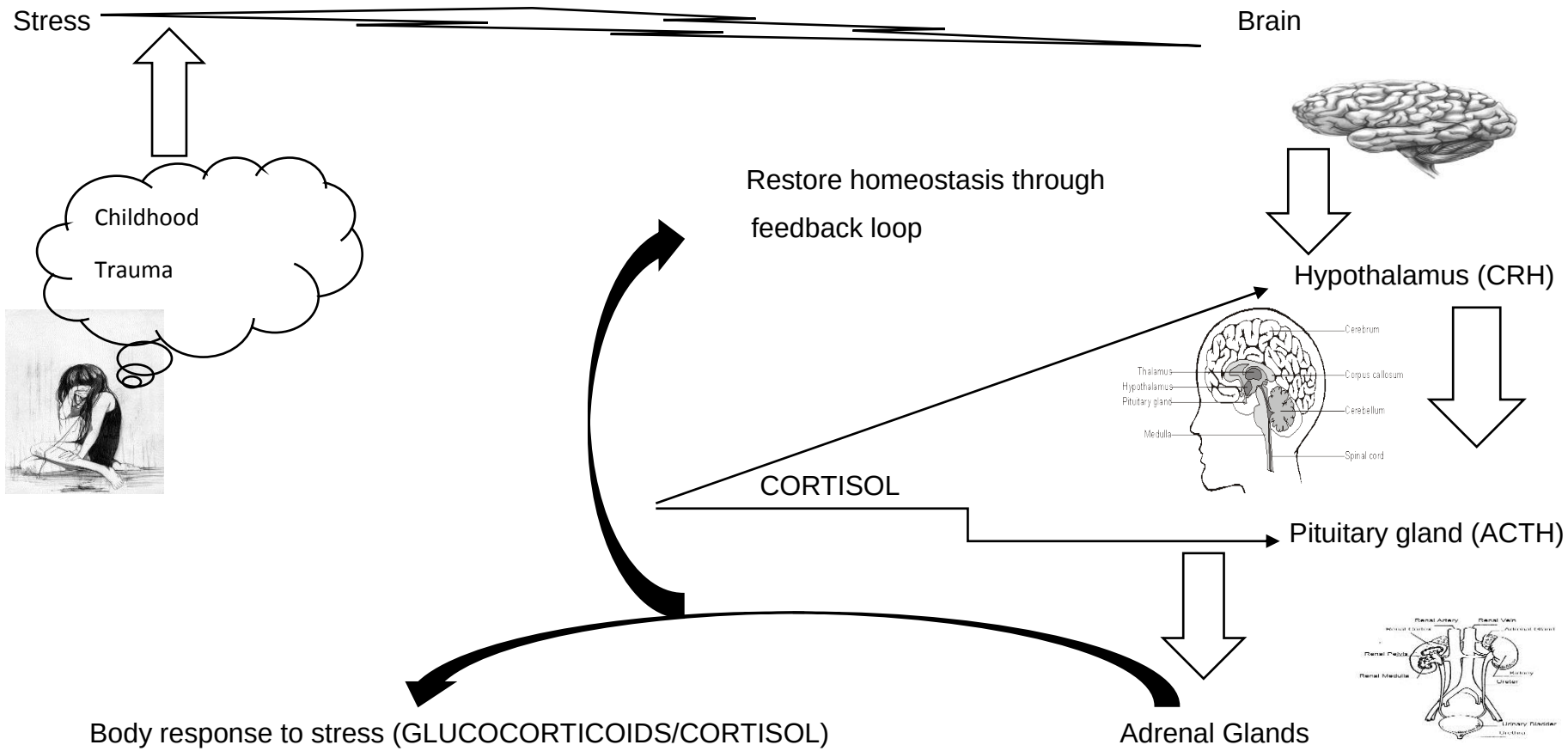


Figure 1.Graphic illustration of the impact of stress on the HPA-axis

APPENDIX B: Childhood Trauma Questionnaire Short Form/English

CTQ–CHILDHOOD TRAUMA QUESTIONNAIRE–Short Form

Participant ID: …… Date: …….. Investigator: ……

	Instructions: These questions ask about some of your experiences growing **up as a child and a teenager**. For each question, circle the number that best describes how you feel. Although some of these questions are of a personal nature, please try and answer as honestly as you can. Your answers will be kept confidential.	**Never True**	**Rarely True**	**Sometimes True**	**Often True**	**Very Often True**
1.	I didn't have enough to eat.	1	2	3	4	5
2.	I knew there was someone to take care of me and protect	1	2	3	4	5
3.	People in my family called me things like "stupid" or "ugly".	1	2	3	4	5
4.	My parents were too drunk or high to take care of me.	1	2	3	4	5
5.	There was someone in my family who helped me feel important or special.	1	2	3	4	5
6.	I had to wear dirty clothes.	1	2	3	4	5
7.	I felt loved.	1	2	3	4	5
8.	I thought that my parents wished I had never been born.	1	2	3	4	5
9.	I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	1	2	3	4	5
10.	There was nothing I wanted to change about my family.	1	2	3	4	5
11.	People in my family hit me so hard that it left bruises /	1	2	3	4	5
12.	I was punished with a belt, a board, or some hard object.	1	2	3	4	5
13.	People in my family looked out for each other.	1	2	3	4	5
14.	People in my family said hurtful or insulting things to me.	1	2	3	4	5
15.	I believe that I was physically abused.	1	2	3	4	5
16.	I had the perfect childhood.	1	2	3	4	5
17.	I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor.	1	2	3	4	5
18.	I felt that some in my family hated me.	1	2	3	4	5
19.	People in my family felt close to each other.	1	2	3	4	5
20.	Someone tried to touch me in a sexual way, or tried to make me touch them.	1	2	3	4	5
21.	Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	1	2	3	4	5
22.	I had the best family in the world.	1	2	3	4	5
23.	Someone tried to make me do sexual things or make me watch sexual things.	1	2	3	4	5
24.	Someone molested me.	1	2	3	4	5
25.	I believe that I was emotionally abused.	1	2	3	4	5
26.	There was someone to take me to the doctor if I needed it.	1	2	3	4	5
27.	I believe that I was sexually abused.	1	2	3	4	5
28.	My family was a source of strength and support.	1	2	3	4	5

Afrikaans on other side

APPENDIX C: Childhood Trauma Questionnaire Short Form/Afrikaans

CTQ–KINDERJARE TRAUMA VRAELYS–Verkorte weergawe

Participant ID: …… Date: …….. Investigator: ……

	Instruksies: Die vrae vra jou uit oor van jou ervarings tydens **jou kinder-en tienerjare.** Vir elke vraag, omkring die nommer wat die beste beskryf hoe jy voel. Alhoewel van hierdie vrae van 'n persoonlike aard is, probeer asseblief om dit so eerlik as wat jy kan te beantwoord. Jou antwoorde word vertroulik hanteer.	**Nooit Waar Nie**	**Selde Waar**	**Soms Waar**	**Dikwels Waar**	**Baie Dikwels Waar**
1.	Ek het nie genoeg gehad om te eet nie.	1	2	3	4	5
2.	Ek het geweet daar was iemand wat na my kon omsien en my beskerm.	1	2	3	4	5
3.	Mense in my familie het my dinge genoem, soos "onnosel" en "lelik".	1	2	3	4	5
4.	My ouers was te dronk of te hoog om vir my te sorg.	1	2	3	4	5
5.	Daar was iemand in my familie wat my gehelp het om belangrik of spesiaal te voel.	1	2	3	4	5
6.	Ek moes vuil klere dra.	1	2	3	4	5
7.	Ek het geliefd gevoel.	1	2	3	4	5
8.	Ek het gedink dat my ouers gewens het dat ek nooit gebore was nie.	1	2	3	4	5
9.	Ek was so hard geslaan deur iemand in my familie dat ek 'n dokter moes sien of hospitaal toe moes gaan.	1	2	3	4	5
10.	Daar was Nikes wat ek wou verander omtrent my familie	1	2	3	4	5
11.	Mense in my familie het my so hard geslaan dat dit bloukolle / of merke gelos het	1	2	3	4	5
12.	Ek was gestraf met 'n gordel, 'n plank of 'n harde	1	2	3	4	5
13.	Mense in my familie het uitgekyk vir mekaar.	1	2	3	4	5
14.	Mense in my familie het aan my goed gesê wat my seergemaak en beledig het.	1	2	3	4	5
15.	Ek glo dat ek fisies mishandel was.	1	2	3	4	5
16.	My kinderjare was ideal gewees.	1	2	3	4	5
17.	Ek was so erg geslaan of aangerand dat dit deur iemand soos my onderwyser, buurman of dokter opgemerk was.	1	2	3	4	5
18.	Ek het gevoel dat iemand in my familie my gehaat het.	1	2	3	4	5
19.	Mense in my familie het na aanmekaar gevoel.	1	2	3	4	5
20.	Iemand het probeer om my op 'n seksueele manier te betas of het my probeer dwing om hulle te betas.	1	2	3	4	5
21.	Iemand het gedreig om my seer te maak of het leuens oor my vertel tensy ek iets seksueel met hulle sou doen.	1	2	3	4	5
22.	Ek het die beste familie in die wêreld gehad.	1	2	3	4	5
23.	Iemand het my probeer forseer om seksueele dinge te doen of het my geforseer om na seksueele dinge te kyk.	1	2	3	4	5
24.	Iemand het my gemollesteer.	1	2	3	4	5
25.	Ek glo ek was emosioneel mishandel.	1	2	3	4	5
26.	Daar was iemand om my dokter toe te neem as ek dit nodig gehad het.	1	2	3	4	5
27.	Ek glo ek was seksueel mishandel.	1	2	3	4	5
28.	My familie was 'n bron van bystand en ondersteuning.	1	2	3	4	5

English on other side

APPENDIX D: Premorbid Adjustment Scale PAS

PAS Rating Form Version 1; 15/10/2014

Participant ID: …… Date: …… Investigator: ……

Date of birth: ……

Date of first onset of psychotic symptoms: …….. Age at time of onset of first psychotic symptoms: ……Duration of untreated psychosis (months): …… Date of first psychiatric hospitalization: …… Duration of untreated illness (months): To be used with PAS rating instructions and criteria. Circle corresponding number. Childhood (Ages 6 to 11)

1. Sociability and withdrawal	0	1	2	3	4	5	6
2. Peer relationships	0	1	2	3	4	5	6
3. Scholastic performance	0	1	2	3	4	5	6
4. Adaptation to school	0	1	2	3	4	5	6

Early Adolescence (Ages 12 – 15)

1. Sociability and withdrawal	0	1	2	3	4	5	6
2. Peer relationships	0	1	2	3	4	5	6
3. Scholastic performance	0	1	2	3	4	5	6
4. Adaptation to school	0	1	2	3	4	5	6
5. Social sexual aspects of life during early adolescence	0	1	2	3	4	5	6

Late adolescence (Ages 16 – 18)

1. Sociability and withdrawal	0	1	2	3	4	5	6
2. Peer relationships	0	1	2	3	4	5	6
3. Scholastic performance	0	1	2	3	4	5	6
4. Adaptation to school	0	1	2	3	4	5	6
5. Social sexual aspects of life during adolescence and immediately beyond	0	1	2	3	4	5	6

Adulthood (Age 19 and above)

1. Sociability and withdrawal	0	1	2	3	4	5	6
2. Peer relationships	0	1	2	3	4	5	6
3. Aspects of adult social – sexual life:							
a. Married presently or formerly:	0	1	2	3			
b. Never married, over 30:			2	3	4	5	6
c. Never married, age 20 -29	0	1	2	3	4	5	6

General

1. Education	0	1	2	3	4	5	6
2. Employed or functioning (3years to 6 months)	0	1	2	3	4	5	6
3. Rapidly change in functioning (6 months)	0	1	2	3	4	5	6
4. Regularity job/school (3years to 6 months)	0	1	2	3	4	5	6
5. Establishment of independence	0		2		4		6
6. Global assessment of highest level of functioning	0		2		4		6
7. Social - personal adjustment	0	1	2	3	4	5	6
8. Degree of interest in life	0		2		4		6
9. Energy level	0		2		4		6

APPENDIX E: Life Events Checklist LEC-5/English

Participant ID: …… Date: ……Investigator: ……

LEC-5: Part 1: Listed below are a number of difficult or stressful things that sometimes happen to people. For each event please check one or more of the boxes to the right to indicate that: (a) it *happened to you* personally; (b) you *witnessed it* happen to someone else; (c) *you learned about it* happening to a close family member or close friend; (d) you were exposed to it as *part of your job* (for example, paramedic, police, military, or other first responder); or (e) you're *not sure* if it fits. Be sure to consider your *entire life* (growing up as well as adulthood) as you go the list of events.

Event	*Happened to me*	Witnessed it	*Learned about it*	*Part of my job*	*Not sure*
1. Natural disaster (for example, flood, hurricane, tornado, earthquake)					
2. Fire or explosion					
3. Transportation accident (for example car accident, boat accident, train wreck, plane crash)					
4. Serious accident at work, home, or during recreational activity					
5. Exposure to toxic substances (for example dangerous chemicals, radiation)					
6. Physical assault (for example, being attacked, hit, slapped, kicked, beaten up)					
7. Assault with a weapon (for example, being shot, stabbed, threatened with a knife, gun, bomb)					
8. Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)					
9. Other unwanted or uncomfortable sexual experience					
10. Combat or exposure to a war-zone (in the military or as a civilian)					
11. Captivity (for example, being kidnapped, abducted, held hostage, prisoner of war)					
12. Life- threatening illness or injury					
13. Severe human suffering					
14. Sudden, violent death (for example, homicide, suicide)					
15. Sudden, unexpected death of someone close to you					
16. Serious injury, harm, or death you caused to someone else					
17. Any other very stressful event or experience					

PLEASE COMPLETE PART 2 ON THE FOLLOWING PAGE

Part 2:

A. If you checked anything for #17 in PART 1, briefly identify the event you were thinking of: _____ If you have experienced more than one of the events in PART1, think about the event you consider the *worst event*, which for this questionnaire means the event that currently bothers you the most. If you have experienced only one of the events in PART1, use that one as the worst event. Please answer the following questions about the worst event (check all options that apply): Briefly describe the worst event (*for example what happened, who was involved, etc*).

_____

How long ago did it happen?

How did you experience it?

It happened to me directly

I witnessed it

I learned about if happening to a close family member or close friend

I was repeatedly exposed to details about it as part of my job (for example, paramedic, police, military, or other first responder)

Other, please describe:

Was someone's life in danger?

Yes, my life

Yes, someone else's life

No

Was someone seriously injured or killed?

Yes, I was seriously injured

Yes, someone else was seriously injured or killed

No

Did it involve sexual violence? *Yes/No*

If the event involved the death of a close family member or close friend, was it due to some kind of accident or violence, or was it due to natural causes?

Accident or violence

Natural causes

Not applicable (The event did not involve the death of a close family member or close friend)

How many times altogether have you experienced a similar event as stressful or nearly as stressful as the worst event? *Just once*

More than once (total# of times)

APPENDIX F: Life Events Checklist LEC-5/Afrikaans

Participant ID: …… Date: ……Investigator: ……..

LEC-5: Deel 1: 'n Paar moeilike of stressvolle dinge wat soms met mense gebeur is onderaan gelys. Maak 'n merkie in een of more van die spasies aan die regterkant van die ervarings om aan te dui dat: (a) dit het met *jou persoonlik gebeur*; (b) jy het *aanskou* hoe het dit met iemand anders gebeur; (c) jy het *uitgevind dat dit* met 'n naaste familielid of gehegte vriend gebeur het; (d) jy was daaran blootgestel *as deel van jou werk* (bv. paramedikus, polisie, millitêr of ander eerste noodbystand); of (e) jy is *nie seker* of dit pas nie. Maak seker dat jy jou *hele lewe* in ag neem (kinderjare sowel as volwassenheid) terwyl jy deur die lys van ervarings gaan.

Ervaring	*Met my gebeur*	*Het dit aanskou*	*Gehoor daarvan*	*Deel van my werk*	*Nie seker*
1. Natuurlike ramp (bv. 'n vloed, orkaan, draaistorm, aardbewing)					
2. Vuur of ontploffing					
3. Vervoer ongeluk (bv. motorongeluk, bootongeluk, trein wrak, vliegongeluk)					
4. Ernstige ongeluk by die werk, huis of gedurende 'n ontspanningsaktiwiteit					
5. Blootstelling aan giftige substanse (bv. gevaarlike chemikalieë, bestraling)					
6. Fisiese aanranding (bv. aangeval, geslaan, geklap, geskop, opgefoeter)					
7. Aanranding met 'n wapen (bv. om geskiet te word, gesteek, gedreig met 'n mes, vuurwapen, bom)					
8. Seksuele aanranding (verkragting, poging tot verkragting, geforseer om enige tipe seksuele aksie uit te voer bv. deur dreigemente dat jy skade aangedoen sal word)					
9. Enige ander ongewenste of ongemaklike seksuele ondervinding					
10. Geveg of blootstelling aan oorlogsfront (In die weermag of as 'n landsburger)					
11. Gevangenskap (bv. deur gesteel te word, ontvoering, as gyselaar aangehou, krysgevangene)					
12. Lewensbedreigende siekte of besering					
13. Ernstige menslike marteling					
14. Skielike grusame dood (bv. moord, selfmoord)					
15. Skielike onverwagte dood van iemand na aan jou					
16. Ernstige besering, skade of dood wat jy aan iemand anders veroorsaak het					
17. Enige ander baie stresvolle gebeurtenis of ervaring					

VOLTOOI ASSEBELIEF DEEL 2 OP DIE VOLGENDE BLADSY

Deel 2:A. As jy enige iets gemerk het by #17 in DEEL 1 identifiseer die ervaring waaraan jy gedink het kortliks: _____ Indien jy meer as een ervaring in DEEL 1 beleef het, dink aan die ervaring wat jy beskou as die *ergste ervaring*, wat vir die doel van hierdie vraelys die ervaring is wat jou tans die meeste pla. Indien jy net een van die ervarings in DEEL 1 beleef het, beskou daardie een as die ergste ervaring. Antwoord asseblief die volgende vrae oor die ergste ervaring (*merk alle opsies wat van toepassingis*): Beskryf die ergste ervaring kortliks (bv. wat het gebeur, wie was betrokkeens

_____

Hoe lank terug het dit gebeur?

Hoe het jy dit ervaar?

Dit het direk met my gebeur

Ek het dit aanskou

Ek het gehoor dat dit het gebeur met 'n naaste familielid of 'n naaste vriend

Ek was herhaaldelik blootgestel aan die besonderhede daarvan as deel van my werk (bv. paramedikus, polisie, millitêr of ander eerste noodbystand)

Ander, beskryf asseblief:

Was iemand se lewe in gevaar?

Ja, my lewe

Ja, iemand anders se lewe

Nee

Was iemand resting beseer of het gesterf?

Ja, ek was ernstig beseer

Ja, iemand anders was ernstig beseer of het gesterf

Nee

Het dit seksuele geed ingesluit? *Ja/Nee*

Indien die ervaring die dood van 'n naaste familielid of gehegte vriend insluit, wasdit as gevolg van een of ander ongeluk of geweld, of was dit as gevolg van 'n natuurlike oorsaak?

Ongeluk of geweld

Natuurlike oorsake

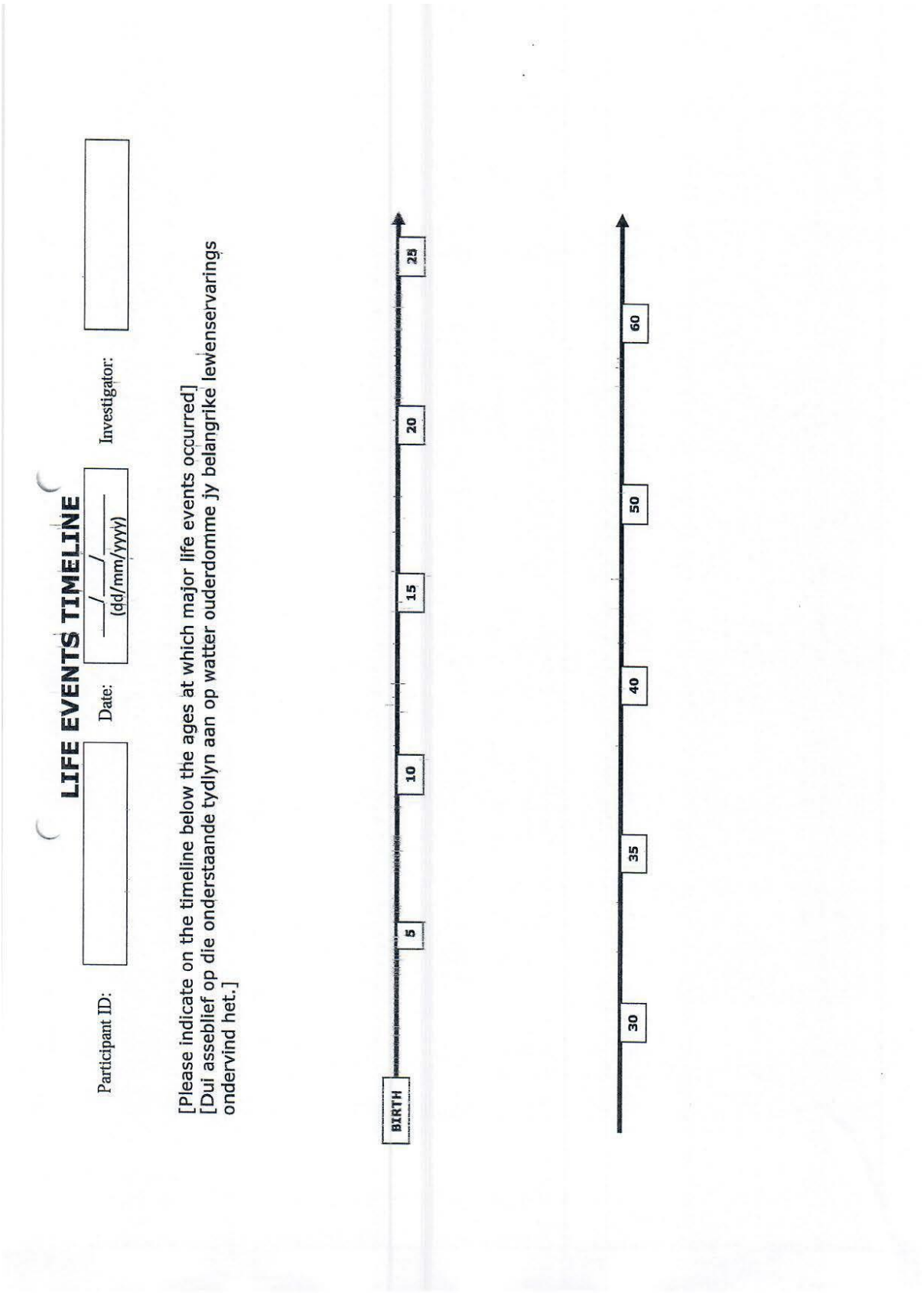
Nie van toepassing (Die ervaring sluit nie die dood van 'n naaste familielid of naaste vriend in nie)

Hoeveel keer altesaam het jy soortgelyke ervarings so stresvol of amper so stresvol as die ergste ervaring beleef?

Net een keer

Meer as een keer (totale # kere)

APPENDIX G: Life Events Timeline



LIFE EVENTS TIMELINE

Participant ID: _____ Date: ___/___/___ (dd/mm/yyyy) Investigator: _____

[Please indicate on the timeline below the ages at which major life events occurred]
[Dui asseblief op die onderstaande tydlyn aan op watter ouderdomme jy belangrike lewenservarings ondervind het.]

BIRTH 5 10 15 20 25

30 35 40 50 60

APPENDIX H: Ethics Approval EONKCS Study

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Approval Letter
Progress Report

23/04/2019

Project ID: 4258

Ethics Reference #: N06/08/148

Title: A prospective study of clinical, biological and functional aspects of outcome in first-episode psychosis in South Africa

Dear Prof Robin Emsley,

Your request for annual renewal of ethics approval received on 16 April 2019 refers. The Health Research Ethics Committee (HREC) reviewed your progress report via expedited review procedures and approved it.

The approval of this project is extended for a further year.

Approval date: 23 April 2019

Expiry date: 22 April 2020

Kindly be reminded to submit progress reports two (2) months before expiry date.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your **Project ID [4258]** and **Ethics Reference Number [N06/08/148]** on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mr. Francis Masiye,

HREC Coordinator,

Health Research Ethics Committee 2.

National Health Research Ethics Council (NHREC) Registration Number:
REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African Department of Health (2006).Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

APPENDIX I: Department of Health Approval EONKCS Study

Verwysing 24/1
Reference
Isalathiso

Navrae Mr J P M Visser
Enquiries
Imibuzo

Telefoon 021 940 4403
Telephone
Ifowuni

Departement van Gesondheid
Department of Health
iSebe lezeMpilo

16 February 2007

Dr Bonga Chiliza
Senior Specialist
Stikland Hospital
Bellville
7530

RESEARCH PROJECT ; FIRST EPISODE PSYCHOSIS STUDY

1. As discussed at the Exco Committee meeting that was held on 13 February 2007 the necessary approvement was granted for the research project as long as the hospital has no expenses or charges.

2. You are requested to keep to the conditions as discussed.

Good luck with the project, looking forward to the results.

.....
MR J P M VISSER
SENIOR MEDICAL SUPERINTENDENT(ACT)

STIKLAND HOSPITAL/HOSPITAAL
De la Haye Avenue, De la Haye, Bellville 7530
Private Bag X13, Bellville 7535
De la Hayeweg, De la Haye, Bellville 7530
Privaatsak X13, Bellville 7535
Tel: (021) 940 4400 Fax: (021) 940 4559

APPENDIX J: Ethics Approval Shared Roots Study

Progress Report

Approval Letter Progress Report

23/08/2019

Project ID: 2334

Ethics Reference No: N13/08/115

Project Title: Understanding the SHARED ROOTS of Neuropsychiatric Disorders and Modifiable Risk Factors for Cardiovascular Disease

Dear Prof Soraya Seedat,

Thank you for your request for extension/annual renewal of ethics approval dated 07 July 2019 and the response to modifications dated 22/08/2019 16:35.

The Health Research Ethics Committee reviewed and approved the annual progress report through an expedited review process. The approval of this project is extended for a further year.

Approval date: 23 August 2019

Expiry date: 22 August 2020

Kindly be reminded to submit progress reports two (2) months before expiry date.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your Project ID [2334] and ethics reference number [N13/08/115] on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mr. Francis Masiye, HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number: REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372

Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number: IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; *the South African Department of Health (2006).Guidelines for Good* Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); *as well as the Department of Health*

(2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and / or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

APPENDIX K: Department of Health Approval Shared Roots Study

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857: fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: RP 003/2014
ENQUIRIES: Ms Charlene Roderick

Department of Psychiatry
PO Box 19063
Tygerberg
7505

For attention: **Prof Soraya Seedat, Prof Robin Emsley, Dr Sian Hemmings, Prof Soraya Bardien, Prof Jonathan Carr, Prof Louise Warnich, Dr Junaid Gamieldien, Prof Christine Lochner, Dr Laila Asmal, Dr Bonga Chiliza, Dr Leigh van den Heuvel and Dr Stéfan du Plessis**

Re: Understanding the SHARED ROOTS of Neuropsychiatric Disorders and Modifiable Risk Factors for Cardiovascular Disease

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

Stikland Hospital **C Bernardo** **Contact No. 021 938 9227**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. The reference number above should be quoted in all future correspondence.

We look forward to hearing from you.

Yours sincerely

DR NT Naledi
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 16/01/2014

APPENDIX L: Ethics Approval Masters Dissertation

Approval Notice New Application

10/06/2019

Project ID: 9783

HREC Reference #: S19/05/098

Title: The association between premorbid adjustment and childhood adversity in first episode schizophrenia

Dear Mrs. Anna Smit,

The **New Application** received on 21/05/2019 14:51 was reviewed by members of **Health Research Ethics Committee 2 (HREC2)** via **expedited** review procedures on 10/06/2019 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: This project has approval for 12 months from the date of this letter.

Please remember to use your **Project ID [9783]** on any documents or correspondence with the HREC concerning your research protocol. Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications monitor the conduct of your research and the consent process.

After Ethical Review

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC we (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report. The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Wes Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. E approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research. For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/9783

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mr. Francis Masiye, HREC Coordinator, Health Research Ethics Committee 2 (HREC2).*National Health Research Ethics Council (NHREC) Registration Number: REC-130408-012 (HREC1)·REC-230208-010 (HREC2)*

Federal Wide Assurance Number: 00001372

Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number: IRB0005240 (HREC1)·IRB0005239 (HREC2)

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Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

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(FDA) of the Department of Health and Human Services.

APPENDIX M: Ethics Approval of Amendment on Masters Dissertation

UNIVERSITEIT STELLENBOSCH UNIVERSITY

Approval Letter Amendment

22/01/2020

Project ID: 9783

Ethics Reference No: S19/05/096

Project Title: The association between premorbid adjustment and childhood trauma in first episode schizophrenia spectrum disorders

Dear Mrs. Anna Smit

We refer to your amendment request 1 dated 14/01/2020.

The Health Research Ethics Committee (HREC) reviewed and **approved** the amended documentation through an expedited review process.

The following amendment was reviewed and **approved**:

1. To change the study title from: *"The association between premorbid adjustment and childhood adversity in first episode schizophrenia"* to *"The association between premorbid adjustment and childhood trauma in first episode schizophrenia spectrum disorders"*.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your project ID 9783 and ethics reference number S19/05/096 on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mrs. Melody Shana

Coordinator

Health Research Ethics Committee 1

National Health Research Ethics Council (NHREC) Registration Number:

REC-130406-012 (HREC1)•REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0006240 (HREC1)•IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; the South African *Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition)*; as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

APPENDIX N: Consent Form Shared Roots Study

See the attached English version of the consent form below. This consent form is also available in Xhosa and Afrikaans and can be provided on request.

Version 6 Date: 22/10/2016

PARTICIPANT INFORMATION AND INFORMED CONSENT FORM FOR RESEARCH INVOLVING GENETIC STUDIES

RESEARCH PROJECT:

Understanding the SHARED ROOTS of Neuropsychiatric Disorders and Modifiable Risk Factors for Cardiovascular Disease

STUDY REFERENCE NUMBER: N13/08/115

PRINCIPAL INVESTIGATOR: Prof Soraya Seedat

ADDRESS: Department of Psychiatry, Faculty of Medicine and Health Sciences Stellenbosch University

PO Box 19063

Tygerberg Cape Town

CONTACT NUMBERS:

Tel: 021 938 9374 (Prof Soraya Seedat)

Tel: 021 938 9207 (Health Research Ethics Committee at Stellenbosch University) Tel: 021 938 9228 / 9768 (Tygerberg study office)

Tel: 021 910 3605 (Stikland study unit)

We would like to invite you to participate in a research study that involves genetic analysis and possible long-term storage of blood and tissue specimens. Please take some time to read the information presented here which will explain the details of this project. Please ask the study staff or doctor any questions about any part of the project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in anyway whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part initially.

This research study has been approved by the ethics Health Research Ethics Committee at Stellenbosch University and it will be conducted to international and locally accepted ethical guidelines for research, namely the Declaration of Helsinki, and the SA Department of Health's 2004 Guidelines: *Ethics in Health Research: Principles, Structures and Processes.*

What is genetic research?

Genetic material, also called DNA or RNA, is usually obtained from a small sample. Occasionally genetic material is obtained from other sources such as saliva or biopsy specimens. A biopsy is a tiny piece of tissue that is cut out e.g. from the skin or from a lump, to help your doctor make a diagnosis. Genes are found in every cell in the human body. Our genes determine what we look like and sometimes what kind of diseases we may be susceptible to. Worldwide, researchers in the field of genetics are continuously discovering new information that may be of great benefit to future generations and also that may benefit people today, who suffer from particular diseases or conditions.

What does this particular research study involve?

Version 6 Date: 22/10/2016

In a nutshell, this research project will try to identify the genes and disease pathways that cause Parkinson's disease, posttraumatic stress disorder, schizophrenia and metabolic syndrome. Metabolic syndrome is a cluster of features such as increased blood pressure, a high blood sugar level, excess body fat around the waist and abnormal cholesterol levels that occur together and increase the risk of heart disease, stroke and diabetes.

Certain blood tests can help us recognise individuals who have a disease versus those who don't have that particular disease. These tests are often called biomarkers as they are biological markers of a particular disease. Some of these biomarkers are well known, like doing a fasting blood glucose test to see if someone has diabetes. Scientists are constantly searching for new biomarkers that can help us to better understand diseases. These biomarkers are mostly used in experiments and can't yet be used to tell if someone has a disease or not. They however help us to better understand the diseases we study and to be able to improve healthcare in the future. We want to obtain blood samples from all participants to perform biomarker testing. Examples of biomarkers that can be measured in blood include hormones, proteins and enzymes.

The causes of these brain disorders and metabolic syndrome are currently not well understood. Some scientists think that there is a link between these disorders. We want to investigate this and will also try to find out whether there are specific genes and biological pathways that cause these disorders to develop. By studying these biological pathways, we may understand what goes wrong in the affected tissue and this may eventually lead to better and more appropriate treatments for these disorders.

We will use a number of specialized genetic techniques to identify these genes and pathways, such as 'whole exome sequencing' and 'transcriptomics'. Whole exome sequencing will allow us to examine thousands of different genes simultaneously to look for gene defects. Transcriptomics will allow us to determine when and how these genes are switched on and off. We will also take photographs of your brain to see how it functions under different conditions.

Lastly, we will need to obtain a small piece of skin tissue from your grow skin cells called fibroblasts. Later these fibroblasts will be used to create special cells called stem cells which are unique in that they can, under the right growth conditions, be use to grow any type of cell in the body. We will use them to grow brain cell lines as these are the cells affected by your disorder. These cell lines are like copies of your cells but can only exist in the laboratory under special growth conditions. We will use these cell lines only to investigate possible disease pathways and processes involved in Parkinson's disease, posttraumatic stress disorder, schizophrenia and metabolic syndrome. Also, we will only investigate the genes involved in these disorders.

An additional test that we would like to do is hair sampling. Cortisol is one of the hormone our bodies produce in response to stress. Sometimes our bodies can secrete too much or too little cortisol and this can have negative effects on our health. We can now measure cortisol and other hormones in hair samples. This is very useful as we can get an idea of the body's long-term release of these hormones and collecting hair samples is painless and easy to do.

Why have you been invited to participate?

You have been invited to participate as you have been diagnosed with one of the following conditions, Parkinson's disease, post- traumatic stress disorder or schizophrenia. In addition to having one of these brain disorders you

may also have metabolic syndrome. Alternatively, you have been invited to participate to act as a control in the study- in other words you have none of the above diseases and this will allow us to look for differences between those who have these diseases and those who do not.

In order to determine whether there is a link between these brain disorders and metabolic syndrome we will recruit a total of 600 patients. Of these, 300 will have one of the three brain disorders *with* metabolic syndrome and the other 300 will have one of the three brain disorders and *will not have* metabolic syndrome.

You are also invited to participate if you are a caregiver of patients living with schizophrenia that initially participated in the EONKCS study. We would like to collect information on your experiences of caring for a friend or relative with schizophrenia.

What procedures will be involved in this research?

We will need to perform the following procedures on you:

Visit 1: After signing the consent form you will be required to complete a few questionnaires about your specific brain disorder. In females we will do a urine pregnancy test as pregnant individuals will be excluded from the study due to safety concerns. You will also be asked about your medical history and a doctor will perform a brief physical examination. This will take approximately 2 – 3 hours.

Visit 2: You will need to fast the evening and morning prior to this visit. A doctor or nurse will take 40 – 50ml (8 – 10 teaspoons) of blood from you for the genetic studies, biomarker testing and also for various laboratory tests to see if you have metabolic syndrome. These tests include measuring your blood sugar (glucose) and fats in your blood (triglycerides and cholesterol) as well as other tests related to metabolic syndrome. C- reactive protein (CRP) and glycosylated haemoglobin (HbA1c). You will be asked to complete some additional questionnaires related to your health and usual practices, such as diet, exercise and smoking.

We will also take your blood pressure and pulse and do some body measurements (height, weight, waist, hip, upper body and neck circumferences). In addition, if you agree we will take one tiny piece of skin from you, measuring 3mm x 3mm. This will be taken from the forearm. You will not require any stiches. The procedure should take about 30 minutes.

At your second visit we also want to collect a very small sample of your hair, about half the thickness of a pencil (3mm). The hair is taken from the back of your head. We carefully collect together a small group of hairs and tie them together. The hair sample is then cut with scissors as close to the skin as possible. The hair will then be stored and later analysed.

At one of our visits you will undergo neuropsychological testing; this will involve doing tests to access your performance in different skills, such as memory and solving problems.

Visit 3: In a subset of patients, we will require a third visit. At this visit we will take some specialized photos of your brain using a technique known as magnetic resonance imaging (MRI). You will be performing certain tasks in the scanner as well as just relaxing. Before the scanning starts you will be allowed to get used to the environment and the tasks will be explained to you. One of the tasks involves you possible being rewarded with money.

This money will be given to you right after the scan is finished and is over and above the travel money you have already received. For a second task, some participants will also be asked to look at a number of pictures. We will be asking you how each picture makes you feel soon afterward. We will also collect urine samples to test for the presence of certain medications and drugs on the day of the scans. These results will only be used to assist us in seeing if these substances have any effects on the photos we take during the tasks and won't be used for any other reason. The whole scan session will take approximately 1 to 1 ½ hours. Although we do not give the scan results out to all participants, as they are experimental scans not meant for clinical purposes, we will inform you should the scan show something that needs treatment.

Follow-up visit: In a subset of patients, 12 months after the first visit, we need to repeat some of the measures such as taking your blood pressure and measurements and completing some questionnaires again and will require to donate 25ml (5 teaspoons) of blood to test for metabolic syndrome. We will also need to take specialized photos of your brain again. This should take 1 - 1½ hours.

Please note that during any of the above mentioned visits, patients will also have the opportunity, should they provide informed consent, to provide researchers with about 1 teaspoon of stool sample (in a special container). This sample will be used to analyse the microorganisms that are present in your gut. Previous studies have shown that there is an important link between the brain and the gut.

If you are a caregiver none of the above assessments apply to you. You will only be asked to complete a short questionnaire on your experiences of caring for someone with schizophrenia.

Follow-up assessments

We want to repeat all the assessments done initially around 12 and 24 months after your first visit. Repeating the assessments will allow as to get a better indication about how disease risks factors change over time. We will contact you to ask you if you will be willing to return and to set up follow-up appointments at about 11 months and 23 months after your initial assessments.

Are there any risks involved in the research?

There are risks associated with all medical procedures. In this research project you may experience the following:

Visit length: Your visits will all generally be around 3 hours long, so you may get tired at times; we will ensure you have as many breaks during your visit as needed. If any of your visits become too long or you become too tired, we will arrange additional visits with you. Similar to your other visits we will also reimburse you for your travel expenses for these additional visits.

Blood taking: You may experience some pain or bruising at the site where blood is taken. We will attempt to minimise this, using experienced medical practitioners.

Skin biopsy: If you agree to give us a piece of skin, there may be pain at the site where the skin is taken. The sample will be obtained by a process known as a 'punch biopsy'. In this procedure, the skin on your arm will be cleaned and injected with a local anaesthetic in order to minimise the pain. A small round blade will be used, and

one small round piece of skin, about 3mm will be removed. The wound will be covered with ointment and plaster and you will receive instructions on how to care for the wound before you leave. You will be given cream and plaster to cover the site before you leave. The wound usually heals after about 3 days. There will be a small scar at the site where the tissue was removed but this is likely to fade over time. If you experience any redness, intense irritation or a yellowish discharge at the site of the biopsy please phone the study office immediately.

Hair sampling: The main risk of this test is that there may be a small area on your head where the hair was cut that may be visible until it has started growing out again. To reduce the risk, we take the smallest possible sample, or if needed rather take 2 – 3 smaller samples to get enough hair. We also take from the back of the head where the overlying hair will tend to cover the area from which the sample was taken.

Brain imaging: You may experience claustrophobic feelings in the brain scanner, but if that occurs the scanning will be discontinued immediately at your request. When the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. To minimise the possible discomfort associated with this, we will give you some soft earplugs to put in and will also put earphones on so that you can listen to music if you so choose. Should you be performing the picture task, you might find some of the pictures disturbing. You are free to end the task at any time however, should you find the pictures too upsetting.

Stool sample: There is no risk involved in providing a stool sample. For caregivers there are no risks involved.

Are there any benefits to your taking part in this study and will you get told your results?

I we determine that you have metabolic syndrome you and your doctor or GP

…… (Dr's name) will be informed of this finding. This is important as by making changes to your diet and lifestyle and by being more closely monitored by your doctor you could be prevented from having heart disease, a stroke or diabetes in the future. We will also provide you with some lifestyle advice that can assist you in making better choices regarding your health.

Should it become clear that certain abnormalities relating to the microorganisms in your gut can possible be treated through changes in your diet or with probiotic treatment, those options will be discussed with you.

Findings from this study may benefit people with Parkinson's disease, post-traumatic stress disorder or schizophrenia in future.

Sharing your experience as a caregiver will help us as researchers to better understand the lived experience of caregivers. In future this knowledge could assist us in the design of more effective support services for patients living with schizophrenia and their families.

How long will your bloods and tissue be stored and where will it be stored?

The DNA and the RNA extracted from your blood as well as the cells grown from the skin tissue and the blood obtained for biomarker testing will be stored at the Stellenbosch University for 15 years.

We work with other researchers in South Africa and overseas and there is a chance that we may send the DNA, RNA and cells to their laboratories. In the event we will first get permission from Health Research Ethics Committee at Stellenbosch University.

After analysis we will store the remaining hair samples for a maximum of 15 years to allow us to repeat analysis if needed.

If your blood is to be stored is there a chance that it will be used for other research?

Your DNA, RNA and cells will only be used for genetic research that is directly related to Parkinson's disease, post-traumatic stress disorder, schizophrenia and metabolic syndrome. Also if we wish to use your samples for additional research in these fields we will apply for permission to do so from the Health Research Ethics Committee at Stellenbosch University.

The stem cells produced from your skin cells will not be used for any reproductive cloning purposes. This type of work is prohibited by the South African National Health Act 61/2003: 57(1).

If you do not wish your samples to be stored after this research study is completed, you will have an opportunity to request that it be discarded when you sign the consent form.

How will your confidentiality be protected?

We will keep your personal details private and will only identify your DNA, RNA and tissue samples by a unique study number. This will be linked to your personal information on a database that will be protected by a password and will only be available to a few selected researchers. If we share your samples with another laboratory we will only refer to you by your study number.

Will you or your researchers benefit financially from the research?

You will not be paid to take part in this study although your travel expenses may be reimbursed for the visits and follow-up visits at approximately R100 per visit. One of the fMRI tasks that you may be asked to perform involves being rewarded with money depending on how well you perform the task.

As a caregiver you will receive no financial reward for participating.

Additional procedures to be followed only in participants diagnosed with schizophrenia (please note that if you participated in the EONKCS study this section does NOT apply to you and you will not receive treatment from us):

At the end of your first study visit, you will receive Flupenthixol tablets that you will have to take orally, on a daily basis for 7 days. Thereafter you will receive your first Flupenthixol injection, followed by a Flupenthixol injection every 2 weeks for the duration of 3 months. At each visit you will be assessed by a psychiatrist to monitor your progress on the Flupenthixol injection. After 3 months the psychiatrist will refer you to your local community clinic, with a letter requesting the community health workers to proceed with your Flupenthixol injectable treatment. We will follow up on you on a regular basis by telephone contact. If you experience any problems at any time, you can contact Sr. Retha Smit on 021 940 4471 (in hours) or 082 805 8225 (after hours).

All medications may have unwanted side-effects, and your treatment has been known to cause stiffness, unusual movements, weight gain, high blood sugar, high blood fats, breast swelling and lactation (milk production) and

and sexual dysfunction. The possible benefits of participating are that you will receive expert care, you will receive medication free - of charge, and importantly, you will be assisting us to learn more about the illness so that we can provide improved care to you and others in the future.

Important Information: In the unlikely event that this research leads to the development of a commercial application or patent, you or your family will not receive any profits or royalties

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Declaration by participant:

By signing below, I …… agree to take part in a genetic research study entitled 'Understanding the SHARED ROOTS of Neuropsychiatric Disorders and Modifiable Risk Factors for Cardiovascular Disease'.

I declare that:

Ihavereadorhadreadtomethisinformationandconsentformanditiswritteninalanguagewithwhich Iamfluent andcomfortable.

I have had a chance to ask questions and all my questions have been adequatelyanswered.

I understand that taking part in the study is voluntary and I have not been pressurised to takepart.

I have received a signed duplicate copy of this consent form for myrecords.

Important Information: In the unlikely event that this research leads to the development of a commercial application or patent, you or your family will not receive any profits or royalties

Version 6 Date: 22/10/2016

Please initial the options you choose below:

Long term storage of samples

(I have the right to receive confirmation that my request has been carried out)

I agree that my blood, tissue, hair, DNA and RNA samples can be **stored for 15 years,** but I can choose to request at any time that my stored sample be destroyed. My sample will be identified with a special study code that **will remain linked to my name and contact details.**

OR

□ I agree that my blood, tissue, hair, DNA and RNA samples can be **stored for 15 years** after the project is completed, but that is anonymised with all possible links to my identity removed, and that the researchers may then use it for additional research in this or a related ield.Once my sample is anonymised, my rights to that sample are waivered. My sample may be shipped to another laboratory in SA or abroad to be used in other research projects in this or related field.

Permission for skin biopsy:

□ **I give permission** to donate two small pieces of skin for research purposes.

□ **I do not give permission** to donate skin for research purposes.

Permission for hair sample:

□ **I give permission** to donate a small sample of hair for research purposes.

□ **I do not give permission** to donate hair for research purposes.

Permission for stool sample:

□ **I give permission** to donate about 1 teaspoon of stool for research purposes.

□ **I do not give permission** to donate about 1 teaspoon of stool for research purposes.

Version 6 Date: 2/10/2016 CONSENT:

…….. ……

Signature of participant Signature of witness

Signed at (*place*) …… DATE: ……

Declaration by investigator:

I *(name*) ……. declare that:

I explained the information in this document to…….

I encouraged him/her to ask questions and took adequate time to answer them.

I am satisfied that he/she adequately understands all aspects of the research as discussed above.

I did/did not use an interpreter. (If *interpreter is used then the interpreter must sign the declaration below*).

…….. ……

Signature of investigator Signature of witness

Signed at (*place*) ……

DATE: ……..

Declaration by interpreter:

I *(name*) ……. declare that:

I assisted the investigator (*name*) ……... to explain the information in this document to (*name of participant*)

…… using the language medium of Afrikaans / Xhosa.

We encouraged him/her to ask questions and took adequate time to answer them.

I conveyed a factually correct version of what was related to me.

I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her questions satisfactorily answered.

…….. ……

Signature of interpreter Signature of witness

Signed at (*place*) …… DATE: ……..

APPENDIX O: Consent Form EONKCS Study

See the attached English version of the consent form below. This consent form is also available in Xhosa and Afrikaans and can be provided on request.

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PATIENT INFORMATION SHEET

Project title: A Prospective study of clinical, biological and functional aspects of outcome in first-episode psychosis.

PRINCIPAL INVESTIGATOR: PROF RA EMSLEY

ADDRESS: Dept of Psychiatry, Faculty of Health Sciences, Stellenbosch University,

PO Box 19063, Tygerberg 7505, Cape Town

Please read this sheet carefully. It will tell you about the study we are conducting, and help you decide if you want to take part.

What is the study and why are we doing it?

Schizophrenia and the related disorders are chronic, and sometimes disabling illnesses, particularly if they are not treated correctly. We are conducting a study to learn more about the illness, particularly ways of improving the outcome. In order to do so, we plan to study about 80 people with the illness, treat them all with the same medication, and follow them up carefully for one to two years. Medication is often used to treat people with psychiatric conditions, and for your illness it is absolutely necessary. The medicine to be used in this study has been approved for use in your condition in South Africa, and has been used extensively in many countries overseas for a number of years. The compound is called Fluanxol Depot. It is given as an injection every two weeks. Although oral medication (tablets) is also available. There are several benefits to use this long-acting injection. First, ensures that the medication is taken correctly – people often find it difficult to remember to take tablets every day, or sometimes, when they become ill, they don't believe that they need the medication. Also, giving medication by long acting injection may reduce the risk to develop certain side-effects.

The study has been approved by the ethics committee of the University of Stellenbosch.

What happens during the trial?

If you are receiving any treatment at the moment this will be stopped for up to a week before we start treating, you with the new treatment. At each visit you will be asking several questions related to your illness and well-being by the doctor and nurse. These questions come from questionnaires that were developed internationally. During four of your visits, you will meet with the psychologists for a series of pencil and paper tests to measure certain cognitive functions like memory and concentration. Many of these are like normal IQ tests that you may have done at school before. These tests will be done in two sessions of approximately 1 hour each. At some of the visits you will also undergo a physical examination and your blood-pressure and pulse and weight will be taken. At the start, and every three months, after overnight fasting a blood sample will be taken (about 20 ml – two dessert spoons) for testing your blood sugar and fat levels. This is because people with your illness may develop abnormalities of blood sugar and fats, sometimes related to treatment they receive. These procedures are not dangerous but can cause some local pain.

At the first visit, at Month 12 and M24 you will undergo a scan. As the scan is done in a relatively confined space, occasionally people become anxious. This does not happen often, and if you feel anxious, we will spend time allowing you to get used to the surroundings. The scan will require you to lie on your back on a table that will move into the scanning machine for 30 minutes it will take for the scan. During this time, you will be able to close your eyes and rest. You will also be able to talk to the study doctor/assistant at all times during the scan if you should experience any discomfort. The scan is a safe procedure if you have been screened correctly for the presence of any magnetic material on or inside you such as pacemakers, surgical clips and metal objects in the eyes. A formal screen for this will be done at the screening visit by a member of the study steam. When the magnet in the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. At this time, you will feel nothing and the noise is not harmful to you in any way. To minimise the possible discomfort associated with this we will give you some soft earplugs to put in and will also put earphones on so that you can listen to music if you so choose.

A urine sample will also be obtained for testing for methamphetamine and cannabis.

Potential Risks and Benefits

All medications may have unwanted side-effects, and your treatment has been known to cause stiffness, unusual movements, weight gain, high blood sugar, high blood fats, breast swelling and lactation (milk production) and sexual dysfunction. The possible benefits of participating are that you will receive expert care, you receive medication free-of charge, and importantly, you will be assisting us to learn more about your illness so that we can provide improved care to you and others in future.

Costs involved:

Participation in the study will not result in any extra costs to you. You will not be paid for participation in the study, but reasonable transport costs will be reimbursed.

Can I stop doing the trial before it is completed?

We would like you to stay in for the full study period because this gives us more information about your condition. However, you can withdraw from the trial at any time. You do not have to tell us why, and this will not affect the way you are looked after. Also, your doctor can take you out of the trial if he or she thinks you should not continue. Your doctor may also do this if your condition gets worse, or if you have serious unwanted symptoms, or if you stop taking the medication.

What will happen to the information you collect about us?

Any information we collect is kept confidential. Your identity will not be made known. Apart from the doctors and nurses involved in the study, our University Ethics Committee will also have access to the results.

What happens now?

You are free to choose whether or not you want to take part in this study. If you do not, it will not affect the way you are looked after.

Who do I call if I have questions?

You can contact Sister R Smit at 082 805 8225 any time (24 hours per day) for urgent matters. If you would like to discuss something with the doctor, you can use the same telephone number.

Contact details for the local Ethics Committee are:

Chairman, Ethics Committee (Research Committee C), Faculty of Health Sciences, University of Stellenbosch, PO Box 19063, Tygerberg 7505, Cape Town.

Tel: 021 938 9207 Fax: 021 933 6330

Who should not be in the study?

You should not participate in this study if you have a serious medical illness, if you have a drug-abuse problem, if you are being treated with Clozapine or if you are a woman who is pregnant or lactating. If you are unclear of any of these consult your doctor.

Please talk to a family member or a friend before you decide whether you want to take part.

If you wish to take part in this trial, tell your doctor and he or she will make all the arrangements. You are requested to inform your general practitioner of your participation in this trial.

Thank you for reading this. Please keep this information sheet and ask the doctor questions to ensure you fully understand what will happen if you agree to take part in this trial.

CONSENT FORM

I, …….. have read the attached patient information sheet and consent to the study called ‘A Prospective study of clinical, biological and functional aspects of outcome in first-episode psychosis in South Africa’. I understand that the information can be used for research purposes, that all information will be treated strictly confidential and that I may withdraw from the study at any time.

Signed: …….subject

……..date

……..researcher

……..date

ASSENT / CONSENT FORM FOR MINORS

I, ……. have read the attached patient information sheet and consent to the study called ‘A Prospective study of clinical, biological and functional aspects of outcome in first-episode psychosis in South Africa’. I understand that the information can be used for research purposes, that all information will be treated strictly confidential and that I may withdraw from the study at any time.

Signed: ……. subject

……..date

……..parent

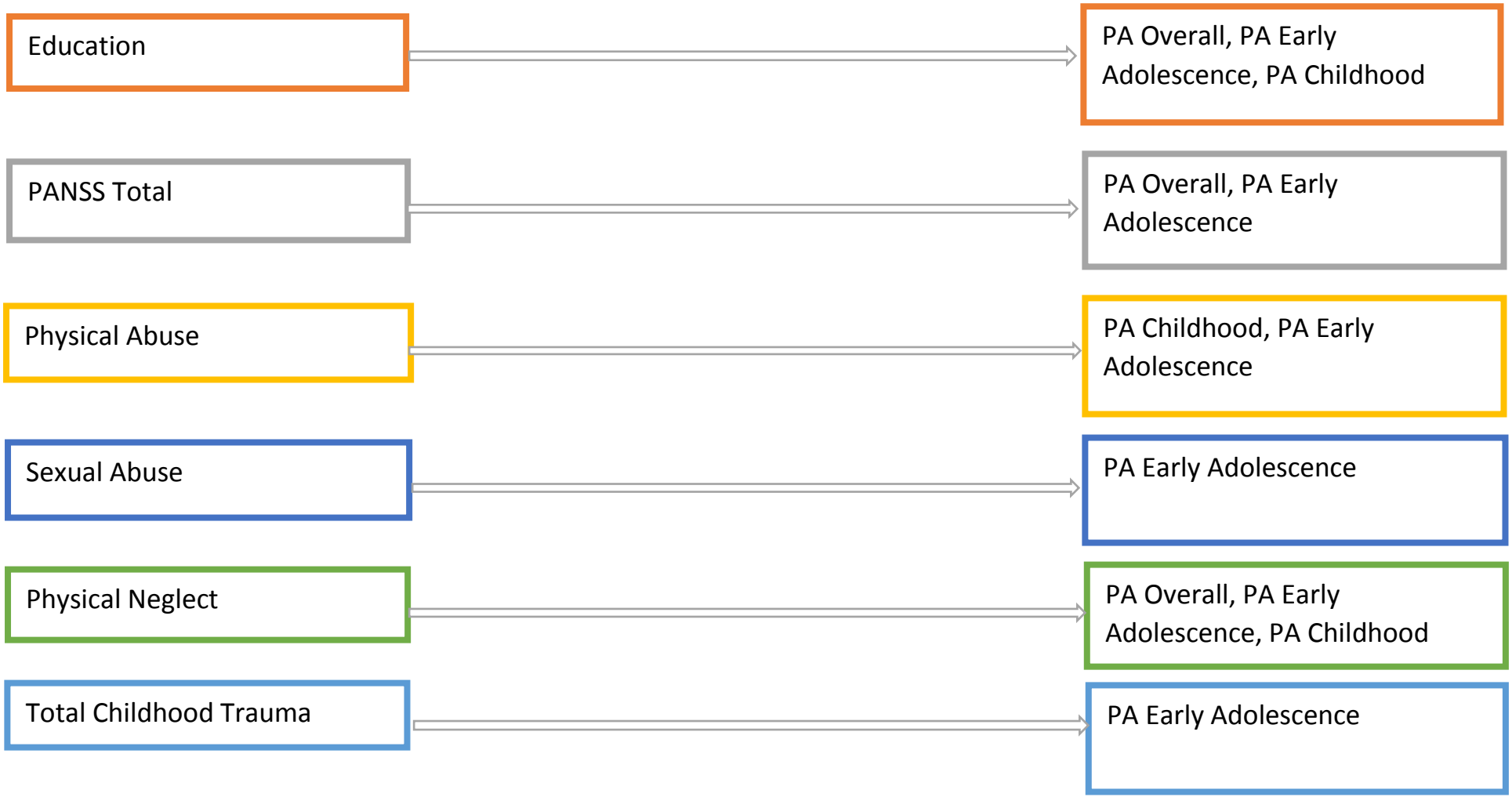
……..date

……..researcher

……..date

APPENDIX P: Supplementary Figure 2

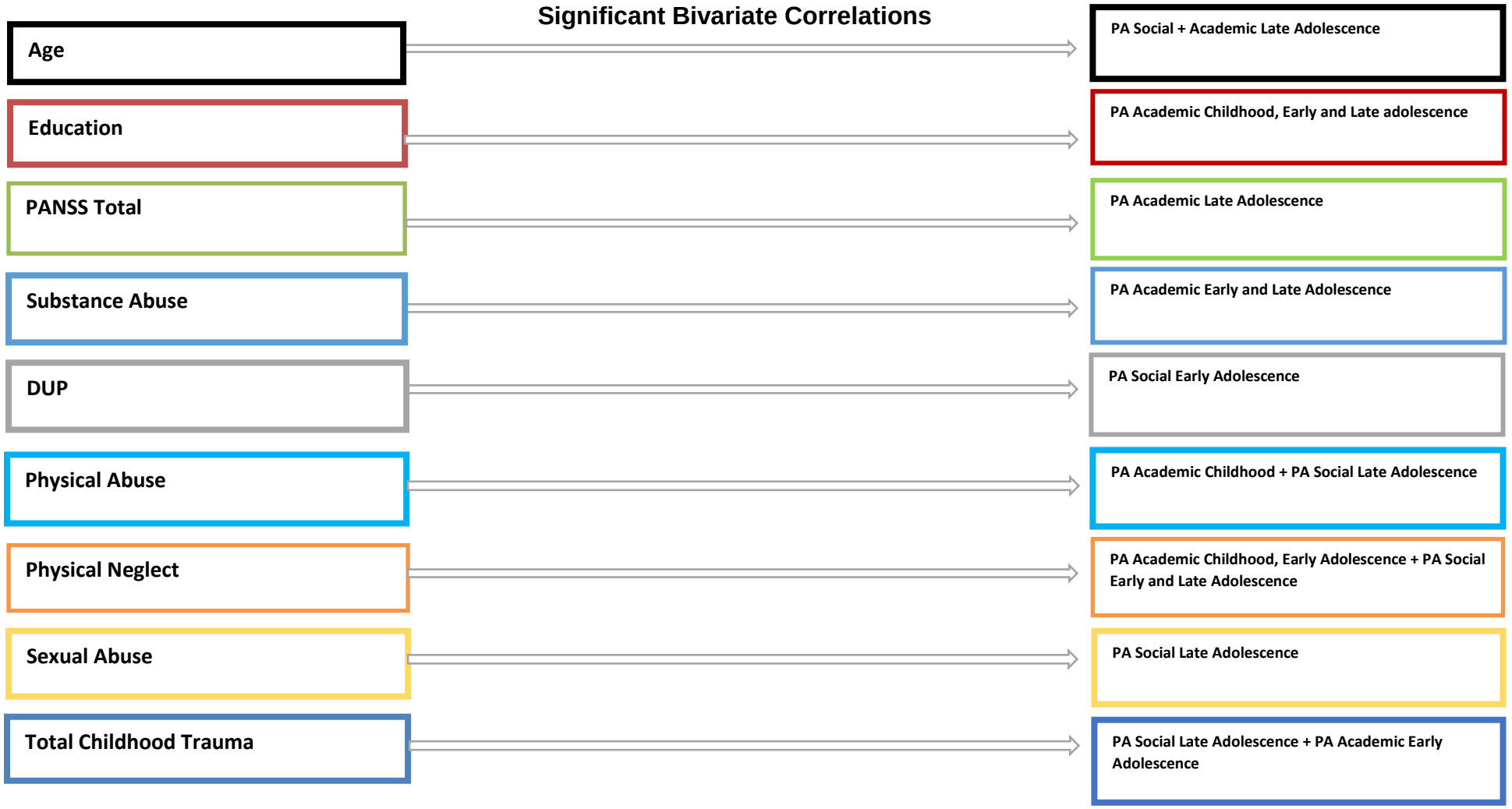
Significant Bivariate Correlations



Significant Relationship between Childhood Trauma and Developmental Period of Premorbid Adjustment

Figure 2.Relationships between childhood trauma and developmental periods of premorbid adjustment

APPENDIX Q: Supplementary Figure 3



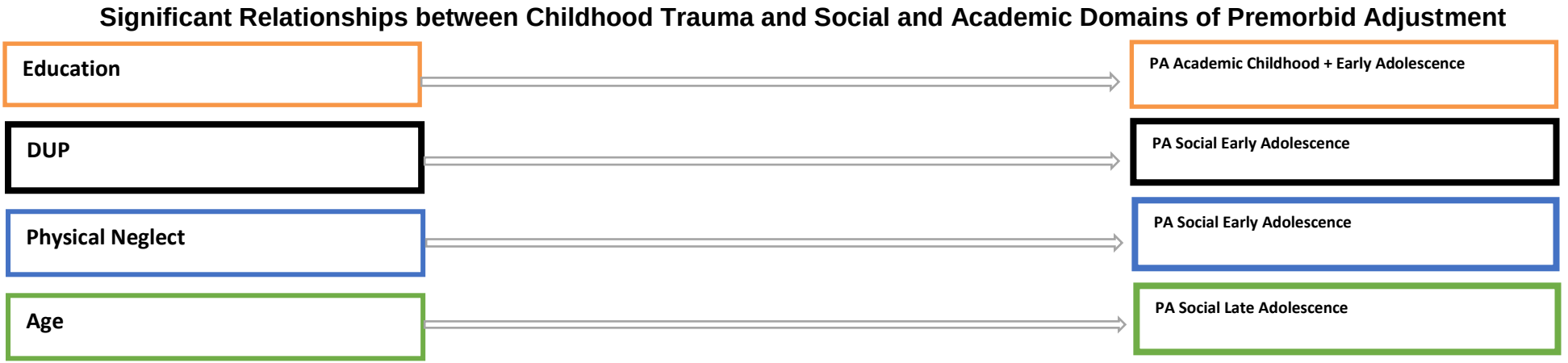


Figure 3.Relationship between childhood trauma and premorbid adjustment domains

APPENDIX R: Frequency of high and low childhood trauma exposure

Childhood trauma subscale	Number	Percentage %	High / Low
Emotional abuse	41	39	High
Physical abuse	34	32	High
Sexual abuse	26	24	High
Physical neglect	38	36	High
Emotional neglect	26	26	High
Overall childhood trauma	52	56	High

APPENDIX S: ANOVA correlations between substance use and premorbid developmental stages

		Sum of squares	*df*	Mean Square	F	Sig
PAS CH social total	Between groups	.006	1	.006	.152	.697
	Within groups	4.485	109	.041		
	Total	4.491	110			
PAS CH academic total	Between groups	.008	1	.008	.252	.617
	Within groups	3.678	109	.034		
	Total	3.686	110			
PAS EA social total	Between groups	.023	1	.023	.615	.435
	Within groups	4.162	109	.038		
	Total	4.186	110			
PAS EA academic total	Between groups	.197	1	.197	4.145	.044
	Within groups	5.027	106	.047		
	Total	5.223	107			
PAS LA social total	Between groups	.012	1	.012	.201	.654
	Within groups	6.291	109	.058		
	Total	6.302	110			
PAS LA academic total	Between groups	.479	1	.479	7.603	.007
	Within groups	6.043	96	.063		
	Total	6.522	97			
	Between groups	.029	1	.029	1.331	.251

PAS overall	Within groups	2.359	109	.022

CH: Childhood; EA: Early adolescence; LA: Late adolescence

APPENDIX T: Declaration of Proofreading and Editing

STELLENBOSCH·UNIVERSITY
your knowledge partner

20 January 2020

To Whom It May Concern

I wish to hereby confirm that I provided the necessary proofreading and editing services to the candidate Anna Margaretha Smit for her Masters dissertation (SU number: 10881476) in my capacity as a research assistant for Stellenbosch University (SU) Department of Psychiatry and member of the Schizophrenia Research Team (SRT) at Stikland Hospital.

I have a background as a junior and then senior writing consultant at the SU Language Centre and Writing Lab, and served there as a consultant from February 2017 until this year. During this time, I also presented academic and dissertation writing workshops both at Stellenbosch and at Tygerberg campus. In addition, I continue to provide an academic writing consultancy in a freelance capacity, with the knowledge of the Doctoral Office at SU Faculty of Medicine and Health Sciences (FMHS). I assisted Retha and provided feedback to my own supervisor and head of the SRT Prof Robin Emsley at a weekly meeting Retha and I both attended. The candidate's supervisor Dr Sanja Kilian also facilitated and had overseen and approved all edits and changes to the final manuscript. I trust that my experience and background as well as the positive initial feedback supports my involvement in writing support and assistance to the candidate.

Sincerely

Dr Hilmar K Luckhoff

MBChB, MPath (cum laude), HonsBSc (pathology) (cum laude)
PhD candidate: Psychiatry

Committed to Optimal Health

Department of Psychiatry

Faculty of Medicine and Health Sciences

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