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DEPARTMENT OF PSYCHIATRY AND MENTAL HEALTH

**Psychological trauma and posttraumatic stress disorder
in a South African birth cohort study**

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ABSTRACT

Introduction

Psychological trauma – including exposure to intimate partner violence (IPV) – is highly prevalent in South Africa, and may result in posttraumatic stress disorder (PTSD) in a subset of individuals. Pregnant women and new mothers are particularly vulnerable; and trauma exposure and PTSD in this sub-group may be associated with a number of adverse maternal-child sequelae including poor birth outcomes and impaired infant neurodevelopment. Risk factors for psychological trauma exposure, and for subsequent PTSD, are likely to include environmental and genetic influences. Given the high burden of trauma and related disorders, the unique genetic ancestry, and the relative paucity of empirical data, further work in South African populations is warranted. This thesis aimed to investigate a number of questions about trauma and PTSD in the Drakenstein Child Health Study (an ongoing South African birth cohort study), including their risk factors, their impact on infant birth anthropometry and development, and their genetic correlations.

Methods

This thesis includes five publications, all presenting data from the Drakenstein Child Health Study. Pregnant women were recruited from two clinics in the Drakenstein sub-district – a peri-urban community outside Cape Town, Western Cape.

Sociodemographic characteristics; psychosocial risk factors (including depression, stressful life events, psychological distress and alcohol and substance misuse); trauma exposure (childhood trauma, IPV and lifetime trauma); and PTSD were assessed using validated and reliable self-reported questionnaires, as well as diagnostic psychiatric interviews. Birth anthropometry and infant neurodevelopmental outcomes were assessed by trained staff. Genotyping was done using the PsychArray BeadChip from

blood DNA. Linear and logistic regression models were used to determine the association between pertinent predictor and outcome variables, controlling for relevant confounders.

Results

Psychological trauma and lifetime PTSD each were found to be highly prevalent in this cohort. Recent life stressors were found to be significantly associated with lifetime trauma; while childhood trauma and recent stressors were significantly associated with PTSD. Maternal trauma exposure was found to increase significantly the risk of poor infant anthropometry at birth. Specifically, mothers who had been exposed to physical IPV during the past year were found to be more likely to deliver an infant with low birthweight; while those reporting lifetime trauma exposure were found to be at increased risk of delivering an infant with reduced head circumference-for-age z-scores (HCAZ) at birth. Maternal trauma exposure and PTSD each were found also to be significantly associated with poor infant neurodevelopment at age 6 months. Infants born to women reporting a history of past-year sexual IPV exposure were found to exhibit poorer fine motor development; while maternal PTSD was found to be significantly associated with poorer fine motor and adaptive behaviour (motor) development. Among the 33 selected single nucleotide polymorphisms (SNPs) genotyped in this cohort, one SNP in the 3'-untranslated region (3'-UTR) of the regulator of the G-protein signaling 2 (*RGS2*) gene, rs4606, was found to be significantly associated with lifetime PTSD after correction for multiple testing.

Conclusion

Maternal trauma exposure and PTSD are highly prevalent in this cohort, and each may affect adversely birth anthropometry and infant neurodevelopment. Environmental risk factors may include childhood or lifetime trauma, and stressful life events; while genetic risk may be conferred by variations in a SNP of the *RGS2* gene. In future, further large-scale transgenerational studies in under-studied populations such as ours are needed to replicate our preliminary findings; and potentially to elucidate the neurobiology of PTSD and the stress response, and inform intervention programmes.

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ABBREVIATIONS AND ACRONYMS

AA	African American
ACTH	Adrenocorticotropin hormone
APA	American Psychiatric Association
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
BDI-II	Beck Depression Inventory II
CI	Confidence interval
CNS	Central nervous system
CRH	Corticotropin releasing hormone
CRHR1	Corticotropin releasing hormone type 1 receptor
CTQ	Childhood Trauma Questionnaire
DCHS	Drakenstein Child Health Study
DoH	Department of Health
DSM	Diagnostic and Statistical Manual
EA	European-American
EPDS	Edinburgh Postnatal Depression Rating Scale
GCP	Good Clinical Practice
GWAS	Genome-wide association study
HC	Head circumference

HCAZ score	Head-circumference-for-age z-score
HIC	High income
HPA	Hypothalamic-pituitary-adrenal
HWE	Hardy-Weinberg equilibrium
IPV	Intimate partner violence
IUGR	Intra-uterine growth restriction
LBW	Low birthweight
LBWR	Low birthweight rate
LD	Linkage disequilibrium
LMIC	Low-middle income
MINI	Mini International Neuropsychiatric Interview
MO	Medical officer
MPSS	Modified Posttraumatic Stress Disorder Symptom Scale
MRC	Medical Research Council
OR	Odds ratio
PACAP	Pituitary adenylate cyclase-activating polypeptide
PC	Principal Component
PGC	Psychiatric Genomics Consortium
PTSD	Posttraumatic stress disorder
RGS2	Regulator of G-protein Signaling 2

SADHS	South African Demographic and Health Survey
SASH	South African Stress and Health Study
SES	Socioeconomic status
SGA	Small-for-gestational-age
SNP	Single nucleotide polymorphism
SNS	Sympathetic nervous system
UCLA	University of California, Los Angeles
UCT	University of Cape Town
UNICEF	United Nations Children's Fund
WAZ score	Weight-for-age z-score
WHO	World Health Organisation

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CHAPTER 1

INTRODUCTION

1.1 Psychological trauma and posttraumatic stress disorder (PTSD) in South Africa

According to nationally representative studies, psychological trauma is highly prevalent in South Africa (Williams et al. 2004). This may be due, in part, to our deep history of political segregation and violence (eg. Truth and Reconciliation Commission 1998), and to our current patterns of urbanization and population transition (Tacoli et al. 2015). The South African Stress and Health Study (SASH) reported that nearly 75% of the sample of 4,351 adult South Africans (who were largely female and Black) had experienced at least one traumatic event in their lifetimes (Williams et al. 2007), and that more than a third had been exposed to some form of violence (Kaminer et al. 2008). The Diagnostic and Statistical Manual, 5th edition (DSM-5) (APA 2013) defines such exposure as:

“Death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows:

- 1) Direct exposure, or
- 2) Witnessing, in person, or
- 3) Indirectly, by learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental, or
- 4) Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (eg. first responders, collecting body parts; professionals repeatedly exposed to details of child abuse).”

Intimate partner violence (IPV) is highly relevant in the South African context, with the SASH reporting a lifetime prevalence of 19% among female participants (Seedat et al. 2009). IPV – and other traumatic events – may be associated with a range of adverse *sequelae*, including health-risk behaviours such as smoking and alcohol consumption (Gass et al. 2010; Jewkes

2002); and mental health disorders and psychopathological symptoms (Gass et al. 2010; Ellsberg et al. 2008; Pico-Alfonso et al. 2006). Posttraumatic stress disorder (PTSD) is a trauma- and stressor-related disorder occurring in a subset of individuals who have been exposed to a traumatic event. According to the DSM-5, PTSD is characterised by intrusive re-experiencing of the index trauma; persistent effortful avoidance of trauma-related stimuli after the event; negative alterations in mood and cognition; and hyperarousal with autonomic hyperactivity (APA 2013) – *see Appendix 1 for full diagnostic criteria (p 177-178)*. These symptoms usually occur within six months of the preceding trauma, and should be present for at least one month before a definitive diagnosis is made. Although the SASH reported a lifetime prevalence of only 2.3% among respondents (Herman et al. 2009), preliminary work by our study group in the Drakenstein Child Health Study maternal cohort (*see Chapter 2 – General Methodology, p 9-21*) has found that approximately a third of participants may be above threshold for PTSD (Koen et al. 2014). Thus, the prevalence and public health burden associated with this disorder may be greater than has been recognised previously. In this chapter, I shall explore briefly the known risk factors (environmental and genetic) of psychological trauma and PTSD, as well as the need for further work in low-middle income (LMIC) settings such as South Africa. Thereafter, I shall provide an overview of the prevalence and transgenerational effects of trauma exposure and PTSD during pregnancy and the peripartum. In each case, I shall outline how the publications included in this thesis will attempt to address the gaps in the current literature. Finally, I shall present the research aim and specific objectives of this thesis.

1.2 Environmental and genetic risk factors for psychological trauma and PTSD

Risk factors for psychological trauma exposure, and for subsequent PTSD are likely to be complex and multifaceted. In two meta-analyses of the predictors of PTSD in adults (Brewin et al. 2000; Ozer et al. 2003), it was found that peritraumatic psychological processes, prior trauma, reported childhood abuse, lack of social support and additional life stress all significantly increased the risk of developing this disorder. Similar findings were reported in a recent systematic review by Ross and McClean (2006), who found that a history of prior mental health disorders (particularly major depression or generalised anxiety disorder) (Loveland et al.

2004; Czarnocka & Slade 2000; Wijma et al. 1997), as well as recent or lifetime trauma (such as sexual assault) (Loveland et al. 2004), may increase the risk of PTSD during pregnancy and the peripartum. While such work is helpful in providing summarised and composite data in this field, similar studies from developing countries are relatively rare. In this thesis, I shall present data from an ongoing South African birth cohort study – the Drakenstein Child Health Study. One research focus will be the prevalence of and risk factors for psychological trauma and PTSD in this cohort (*Chapter 3 – Publication 1, p 22-41*).

Although it has been hypothesised that PTSD may be a normal response to unusually severe trauma (eg. Yehuda & McFarlane 1995), it is clear that not all traumatised individuals develop PTSD – a paradigm echoed in animal models of this disorder (Cohen et al. 2012). Further, as PTSD is the only psychiatric disorder requiring an environmental impact for diagnosis, it is most likely to be understood as a function of environmental factors interacting with genetic vulnerability. To date, family, twin and molecular studies have built a convincing case for heredity in the pathogenesis of PTSD. This disorder has an estimated heritability of 30% to 46% (Skelton et al. 2012; Sartor et al. 2011, 2012; Brewin et al. 2000; True et al. 1993; Koenen et al. 2008b). Specific candidate genes found to confer risk include those in systems known to underlie the neurobiology of PTSD, such as the hypothalamic-pituitary-adrenal (HPA) axis. However, there remain little data on populations of African ancestry, the genomic structure of which is ancient and more varied. This thesis will attempt to address this gap in the literature by investigating the association between published PTSD candidate genes and the development of PTSD among traumatised women in the Drakenstein cohort (*Chapter 7 – Publication 5, p 116-138*).

1.3 Psychological trauma and PTSD during pregnancy and the peripartum

There is a compelling body of work documenting gender-specific differences in the aetiology, heritability, diagnosis and clinical presentation of trauma exposure and PTSD (Herman et al. 2009; Kessler et al. 1995; Sartor et al. 2011; Darensburg et al. 2006; Ressler et al. 2011; Cohen et al. 2011; Olff et al. 2007; Williams et al. 2004; Tolin & Foa 2006). Overall, females – particularly pregnant women and new mothers – have been found to be a highly vulnerable

subgroup (eg. Beck et al. 2011). In their systematic review, Ross and McClean (2006) reported a higher prevalence of PTSD during pregnancy (7.7% in one study – Loveland et al. 2004) than has been reported in the general South African population (eg. Herman et al. 2009). Exposure to psychological trauma and PTSD during pregnancy and the peripartum is likely to exert deleterious effects both on mother and child. For example, in their sample of 101 women seeking prenatal care in Oahu, Hawaii, Morland and colleagues (2007) found that women with PTSD entering pregnancy were more likely to engage in high-risk health behaviours such as smoking, alcohol consumption, substance use and poor prenatal care. Further, in their study of 1,100 pregnant women recruited from obstetric clinics in inner-city New Haven, Connecticut, USA, Rogal and colleagues (2007) found that PTSD was significantly associated with increased odds of spontaneous abortion, preterm contractions and ectopic pregnancy. Exposure to IPV (Murphy et al. 2001) or PTSD (Seng et al. 2011) during pregnancy each have been found also to be associated with low infant birthweight. Further work on the effects of maternal trauma exposure or PTSD on birth outcomes is highly relevant in settings such as ours, given the high-risk profile of mothers and children (UNICEF South Africa 2013). Thus, a third research focus of this thesis will be on the association between trauma or PTSD, and altered infant anthropometry at birth (*Chapter 3 – Publication 1, p 22-41; Chapter 4 – Publication 2, p 42-72*).

Loss of developmental potential in infancy is of particular concern in developing countries such as South Africa, as it has been estimated that more than 200 million children under 5 years fail to reach their potential in cognitive development in this setting (Grantham-McGregor et al. 2007; Walker et al. 2007, 2011; Engle et al. 2007, 2011; Lake 2011). This loss of potential is an indicator of the discrepancy between the current developmental level of a child, and the projected achievement that a he or she may have been expected to attain in a more nurturing, stimulating environment (Grantham-McGregor et al. 2007). While there is evidence that PTSD may increase the risk of emotional regulation difficulties in infancy (Enlow et al. 2011); and that exposure to prenatal stress may affect adversely infant developmental outcomes (eg. Buitelaar et al. 2003; Laplante et al. 2008), no published work to date has investigated specifically the association between maternal PTSD and poor infant neurodevelopment. This provides a fourth

important research question, which will be addressed in *Chapter 5 – Publication 3 (p 73-99)*; and *Chapter 6 – Publication 4 (p 100-115)*.

1.4 Overview of thesis

This will be a composite body of work including five publications, each reporting data from the ongoing Drakenstein Child Health Study (*see Chapter 2 – General Methodology, p 9-21*).

1.5 Study aim

This thesis aims to address various questions about trauma and PTSD in the South African context, including their prevalence in pregnant women, their impact on infant birthweight and development, and their genetic correlations.

1.6 Study objectives and related publications

As outlined above, there are four important gaps in the current literature, prompting five key research objectives:

Objective 1:

To investigate risk factors for maternal trauma and PTSD, and their association with adverse birth outcomes, in a cohort of mother-infant dyads in the Drakenstein sub-district, Western Cape, South Africa.

Publication 1:

Koen N, Brittain K, Donald KA, Barnett W, Koopowitz S, Maré K, Zar HJ, Stein DJ (2015) Psychological trauma and posttraumatic stress disorder: an exploratory investigation of risk factors and associations with birth outcomes in the Drakenstein Child Health Study. *European Journal of Psychotraumatology*. In review.

Objective 2:

To determine the prevalence of maternal trauma exposure (including IPV), and its association with low infant birthweight in the study cohort.

Publication 2:

Koen N, Wyatt GE, Williams JK, Zhang M, Myer L, Zar HJ, Stein DJ (2014) Intimate partner violence: associations with low infant birthweight in a South African birth cohort. *Metabolic Brain Disease* 29(2):281–299.

Objective 3:

To determine the association between maternal trauma exposure and poor infant neurodevelopment at age 6 months in the study cohort.

Publication 3:

Koen N, Donald KA, Wyatt GE, Zhang M, Myer L, Koopowitz S, Barnett W, Marais A, Adnams CM, Zar HJ, Stein DJ (2015) Prenatal alcohol use, intimate partner violence and other psychiatric symptoms and stressors as predictors of poor developmental outcomes in infancy in a South African birth cohort. *Journal of Health Psychology*. In review.

Objective 4:

To determine the association between maternal PTSD and poor infant neurodevelopment at age 6 months in the study cohort.

Publication 4:

Koen N, Brittain K, Donald KA, Barnett W, Koopowitz S, Maré K, Zar HJ, Stein DJ (2015) Maternal posttraumatic stress disorder and infant developmental outcomes at age 6 months in the Drakenstein Child Health Study. *British Journal of Psychiatry*. 2015. In review.

Objective 5:

To determine the association between variants in specific candidate genes (which previously have been identified as being associated with the stress response and PTSD), and PTSD in this cohort.

Publication 5:

Koen N, Lori A, Koopowitz S, Maré K, Ramesar R, Zar HJ, Ressler KJ, Wingo AP, Stein DJ (2015) Association between *RGS2* and posttraumatic stress disorder in a female cohort: results from the Drakenstein Child Health Study. *Acta Neuropsychiatrica*. In submission.

The hypotheses of this thesis are as follows:

- a) We expect to find a notable prevalence of psychological trauma and of PTSD in this study sample.
- b) We expect to find significant associations between all or some of the known environmental risk factors, and/or the known stress-related genetic polymorphisms, with the presence of PTSD.
- c) We expect to find notable associations between maternal trauma and/or PTSD, and adverse birth and infant outcomes.

Despite the high burden of psychological trauma, the notable prevalence of PTSD, and the adverse intergenerational effects of maternal exposure to trauma and PTSD in LMIC countries such as South Africa, there remains a relative dearth of research emerging from these settings. Further, populations of African ancestry remain under-represented in work on the genetics of PTSD and related disorders. Thus, studies such as those included in this thesis are warranted not only to enhance the neurobiological and scientific understanding of this disorder, but also potentially to inform public health and therapeutic interventions. Transgenerational studies are of particular relevance, as these may be key to improving long-term infant and child health and development.

The next chapter will provide an overview of the Drakenstein Child Health Study, as well as methodological details relevant to the thesis as a whole. Chapters 3 to 7 each will comprise a publication which addresses a specific research objective (1-5), as outlined above. Finally, Chapter 8 will present a general discussion for the thesis, including research limitations, recommendations for future work in the field, and concluding comments.

NOTE: Minor adjustments to the format and structure of the original manuscripts have been made in order to maintain consistency, connectedness and clarity throughout this body of work.

CHAPTER 2

GENERAL METHODOLOGY

2.1 Drakenstein Child Health Study: overview

The Drakenstein Child Health Study (DCHS) is an ongoing population-based birth cohort study investigating maternal and child health longitudinally in a poor, peri-urban sub-district in the Western Cape, South Africa, with a focus on paediatric lower respiratory tract infections (Zar et al. 2015). The Drakenstein sub-district is located in Paarl, 60 km outside Cape Town. This study site was selected for its accessibility, population (of stable but low socioeconomic status), high trauma burden and cost-free public health system. It is also close in proximity to academic partners at the University of Cape Town and Red Cross Children's Hospital. Within the DCHS, longitudinal measurements of risk factors in seven key areas that may affect maternal and child health are undertaken, ie. environmental, infectious, nutritional, genetic, maternal, immunological and psychosocial (Zar et al. 2015).

2.2 Study population

The local community comprises approximately 200,000 residents, of primarily low socioeconomic status (Zar et al. 2015). Unemployment and poverty-related risk factors such as malnutrition, alcohol misuse and informal living conditions are rife. The target sample size of 1000 mother-infant dyads was selected on the basis of feasibility and preliminary power analyses. It is anticipated that this study sample will have significant statistical power to detect relative associations of at least 1.5-fold for prevalent risk factors (Zar et al. 2015), and will provide an adequate number of paediatric pneumonia cases (a primary aim of the DCHS).

2.3 Participant recruitment and follow-up

Pregnant women in their second trimester were approached randomly by trained study fieldworkers while awaiting their routine antenatal clinic visits. Participant recruitment occurred at two primary care clinics in the Drakenstein sub-district – TC Newman (serving

primarily a Mixed-Race population) and Mbekweni (serving a mainly black African population). Pregnant women were eligible for enrollment if they were aged 18 years or older, were accessing one of the two primary health care clinics, were not intending to move out of the Drakenstein sub-district within the following year, and signed written informed consent. Thereafter, a number of ante- and postnatal study visits occurred – at these primary care clinics and at Paarl Hospital (at which all births occurred and hospital care was undertaken). Two home study visits were also performed to investigate environmental risk factors. Mother-child dyads will be followed until the children are at least 5 years old (Zar et al. 2015).

2.4 Measures and variable calculation

Comprehensive data including biomedical, environmental, psychosocial, demographic, physical and mental health of the mother-infant dyads are collected as part of the DCHS as a whole. Only those methodological aspects relevant to this thesis will be discussed here, *Appendix 2 (p 179-248)* (see also Koen et al. 2014; Zar et al. 2015; Stein et al. 2015).

a) MATERNAL ASSESSMENT

Sociodemographics

A questionnaire to assess socioeconomic status (SES) was adapted from the version used in the SASH (Myer et al. 2008) and assessed education and income; access to governmental financial assistance; household composition; and available amenities (including electricity, running water, electric stove and a functional telephone). All items are particularly relevant to the LMIC setting and may affect maternal and newborn health and well-being. For the purposes of this study, a composite score of SES was developed. Four sociodemographic variables (as assessed by the SES questionnaire) were used to generate this score, ie. educational attainment; employment status; household income; and assets and market access. Variables were extracted as follows:

- i) Educational attainment: Participants with primary education only scored 0, those with some secondary education scored 1, those who had completed secondary education scored 2, and those with any tertiary education were assigned a score of 3.
- ii) Employment status: This variable was dichotomized, with those currently unemployed scoring 0, and those currently employed scoring 1.
- iii) Household income: Total household income of less than R1,000 per month was scored 0, monthly income between R1,000 and R5,000 was scored 1, and households with an income greater than R5,000 per month were assigned a score of 3.
- iv) Assets and market access: A composite asset index was calculated as the sum of assets/infrastructure and market access. In order to assess assets/infrastructure, participants were requested to indicate the availability of the following household resources and amenities (a score of 1 was assigned for each available item): electricity, a tap or running water, a domestic worker, a flush toilet inside, a built-in kitchen sink, an electric stove or hotplate, a working telephone (including cellphone), at least one motor car or truck, a motorcycle or scooter, and/or a bicycle. The composite score for assets/infrastructure was then obtained by summing the individual item scores. Similarly, the total market access score was assessed by the following questionnaire items: shopping at supermarkets, using any financial services (such as bank account, ATM card or credit card) and/or having an account at a retail store (eg. Pep). Again, each affirmative item was assigned a score of 1, and the total market access score derived by adding these individual scores.

The grand total SES score was then generated as follows:

$$\begin{aligned}
 \text{Composite SES score} = & \text{standardised income} \\
 & + \text{standardised education} \\
 & + \text{standardised assets} \\
 & + (0.5 \times \text{employment})
 \end{aligned}$$

Participants were stratified into quartiles based on their relative SES score, ie. lowest, low-moderate, moderate-high, and highest SES. These quartiles were generated for the purposes of this study and represent an internal comparison for the study sample.

Planning of birth and partner support

The Planning of Birth/Partner Support Questionnaire was developed for this study and adapted from questions used in the SASH (Myer et al. 2008) to assess the effect of varying degrees of social support in pregnant women. Partner support and reliability were assessed on a likert scale from 1 (“not at all”) to 5 (“extremely”), with higher scores indicating greater support and reliability. A continuous measure was generated based on a number of items which assessed broadly pregnancy intention, contraceptive use at the time of becoming pregnant, and support received from the partner. Responses were then scored as either affirmative (1), indicating a greater degree of birth planning and/or support; or negative (0). Thus, the higher the continuous score, the lower the maternal risk profile.

Life stressors, trauma exposure and PTSD

The World Mental Health Life Events Questionnaire is a 17-item tool which assesses exposure to stressful/negative life events during the past 12 months. The questionnaire used in this study was adapted from those used in the SASH (Myer et al. 2008). Individual items were scored as either “0” (having not occurred) or “1” (having occurred). A total score was then obtained by summing the total number of life events that participants reported experiencing during the prior 12 months, with higher scores indicating greater exposure to stressful life events.

The Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1994) is a 28-item inventory assessing three domains of childhood abuse (sexual, physical, and emotional), and two domains of childhood neglect (physical and emotional), occurring at or before the age of 12 years. This questionnaire has shown excellent sensitivity and specificity in the classification of childhood abuse and neglect. A five-point frequency of occurrence scale is utilized as follows: (1) never true, (2) rarely true, (3) sometimes true, (4) often true, and (5) very often true. Thus, each subscale is scored on a spectrum from 5 (no history of abuse or neglect) to 25 (very extreme history of abuse and neglect). Three items are included also as a Minimisation/Denial scale to detect potential under-reporting of abuse by participants. These items are dichotomised (ie. a response of “never” is scored 0; all others are scored 1) and added, with a sum total ≥ 1

indicating possible under-reporting (Bernstein & Fink 1998; Villano et al. 2004). In our sample, participants were allocated a total continuous score by summing individual items (excluding those comprising the Minimization/Denial scale). Higher scores signified greater severity of abuse. Further, participants were dichotomised into those with a history of childhood trauma, and those without. Cut-off scores for each clinical domain as defined in the CTQ manual (Bernstein & Fink 1998) were used. Participants scoring within the “none or minimal” range were defined as below threshold for a history of childhood trauma; those in any other category (ie. “low to moderate”, “moderate to severe” or “severe to extreme”) were defined as above threshold.

The Intimate Partner Violence (IPV) Questionnaire used in this study was adapted from the WHO multi-country study (Jewkes 2002) and the Women’s Health Study (Zimbabwe) (Shamu et al. 2011) and assessed lifetime and recent (past-year) exposure to emotional, physical and sexual abuse. Emotional abuse was assessed by the following items: being insulted or made to feel bad about oneself; being belittled or humiliated in public; being purposefully scared or intimidated; and being threatened. To assess physical abuse, women were asked about a history of having been slapped or having had something thrown at them which could hurt them; being pushed or shoved; being hit with a fist or with something else that could hurt them; being kicked, dragged, beaten, choked or burnt; and being threatened with or actually abused with a gun, knife or other weapon. Finally, sexual abuse was defined as having been physically forced to have sex when one did not want to; having sex with one’s intimate partner when one did not want to out of fear of what he might do; and/or having been forced to do something sexually that was degrading or humiliating. A four-point frequency of occurrence scale was used: (1) never, (2) once, (3) few times, and (4) many times. Scoring guidelines were devised for the purposes of this study, and were based on prior work in similar South African studies (Dunkle et al. 2004). Participants were categorised as having had no exposure to IPV if all responses were “never”; having an isolated incident of IPV if one response was “once”; a low frequency of violence if they responded “once” to more than one item; a mid-frequency if they responded “a few times” to at least one item, but did not respond “many times” to any item; and a high frequency if there were any responses of “many times” in the questionnaire. In

addition, those who responded that the violence had occurred during the past 12 months were categorised as having experienced recent (past-year) violence and dichotomised as “above threshold” for recent IPV, versus those below threshold, ie. with no recent exposure.

Participants were also allocated continuous scores by summing individual items.

The Modified Posttraumatic Stress Disorder Symptom Scale (MPSS) (Foa et al. 1993) is a 17-item interview that was used as a rapid screening tool for PTSD in our study population. This tool mirrors the DSM-IV criteria for PTSD (APA 2000) and has shown good psychometric properties with concurrent validity. The MPSS was selected for use in this study due to its reasonably good diagnostic validity for PTSD. Participants were requested to respond to each item on a four-point frequency scale, from 0 (absence of symptom) to 3 (symptom occurs five or more times per week/very much/almost always). A final item was included to assess for duration of symptoms, with response options including < 1 month; 1 – 3 months; 3 months – 1 year; and > 1 year. As no MPSS cut-off score for PTSD has been established clearly (Binder et al. 2008), the DSM-IV criteria were applied to the MPSS items to generate a proxy variable for PTSD diagnosis. Those items assessing the re-experiencing symptom cluster were scored as “above threshold” if their sum totaled ≥ 1 ; avoidance/emotional numbing ≥ 3 ; and increased arousal ≥ 2 . Participants who scored above threshold across all three symptom clusters, and reported symptom duration of at least 1 month (scored ≥ 1 for item 18) were classified as “suspected PTSD cases”.

The Mini International Neuropsychiatric Interview (MINI) is an abridged version of the Structured Clinical Interview for DSM-IV (Lecrubier et al. 1997; Sheehan et al. 1997, 1998). This clinician-administered interview was used to obtain a more detailed phenotypic description of trauma exposure (as defined by the DSM-5 criteria (APA, 2013)) and of lifetime PTSD in this study sample, from a number of ante- and postnatal timepoints. Based on their responses to the MINI items, participants were categorised as having no trauma exposure; being trauma-exposed with no PTSD; and being trauma-exposed with PTSD.

Psychological distress and depression

The SRQ-20 (Harding et al. 1980; Scholte et al. 2011) is a WHO-endorsed measure of psychological distress that has been used widely in international and South African settings, and has shown good reliability and high face validity (Harpham et al. 2003; Tuan et al. 2004; Rumble et al. 1996). The SRQ-20 comprises twenty items, intended to assess for the presence of non-psychotic symptoms, including symptoms of depressive and anxiety disorders. These items were selected on the basis of a number of psychiatric assessment tools used in four different LMIC countries (Mari & Williams 1986). Symptoms of depressive and anxiety disorders, as described in the DSM-IV, are included in the SRQ-20. Participants were required to respond in the affirmative (scored 1) or negative (scored 0) for each item. For our purposes, individual item scores were summed to obtain total continuous scores. Further, participants were dichotomised as “high risk” (SRQ score > 8) or “low risk” (score ≤ 8). While cut-off points vary in different cultural and geographical settings, the threshold score of 8 is used widely (Ventevogel et al. 2007; Harpham et al. 2003).

The Beck Depression Inventory II (BDI-II) is a commonly-used and reliable screen for depressive symptoms (Beck et al. 1961, 1988, 1996a,b). The BDI-II has shown good validity and internal consistency, for both psychiatric and non-psychiatric subjects (Beck et al. 1988, 1996b; Sprinkle et al. 2002). Further, this tool has been validated in a low-income African-American sample with similar sociodemographic characteristics as our own (Grothe et al. 2005) and has been used in a number of studies conducted in South Africa (Kagee et al. 2014; Nel & Kagee 2013; Kagee & Martin 2010). The BDI-II comprises 21 items, each assessing a symptom described in the DSM-IV criteria for major depression. All items require participants to select one of four options, scored on a severity scale from 0 (absence of symptom) to 3 (severe symptom, often with functional impairment) and pertaining to the two weeks prior to the assessment, including the day of questionnaire administration. Total scores are then obtained by summing individual item scores. In an early publication, Beck and Beamesdefter (1974) stated that BDI scores should not be adhered to strictly for diagnostic status. Rather, scores less than 10 should suggest the absence of a depressive disorder; those between 10 and 19, mild to moderate

depressive symptoms; between 19 and 29, moderate to severe symptoms; and that scores greater than 30 should indicate severe depression. These authors also recommended that a threshold score of 12 – 13 would be appropriate for identifying depression in psychiatric patients, while a score of 9 – 10 could be used in medical patients (Beck & Beamesdefe 1974; Lasa et al. 2000). For our purposes, BDI-II scores were taken as continuous measures (with higher scores indicating more severe depressive symptoms), as well as dichotomous variables. A cut-off score of ≥ 20 was used for dichotomising participants into “probable moderate/severe clinical cases” versus “probable sub-threshold participants”, as has been described elsewhere (Lasa et al. 2000).

The Edinburgh Postnatal Depression Rating Scale (EPDS) (Cox et al. 1987) is a 10-item self-report measure of recent depressive symptoms, which has shown good psychometric properties in validation studies (Eberhard-Gran et al. 2001). This tool was developed originally for use in postnatal women, under the assumption that normal symptoms experienced during the perinatal period (eg. sleep and appetite changes) could be misattributed to a depressive disorder on many of the standard screening tools (including the BDI-II). The EPDS assesses for the presence of mood changes characteristic of postnatal depression, within the week preceding questionnaire completion. Each item is scored on a frequency scale, ranging from 0 to 3. As for the other measures of depression in this study, a continuous score was obtained by summing the individual items; the higher the score, the greater the symptom severity. Further, participants were classified as “probable cases” if they scored > 13 on the EPDS. This threshold has been used in similar studies conducted in the South African LMIC context (Hartley et al. 2011).

Substance use

Substance use in this study sample was assessed using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). This tool was developed by the World Health Organisation (WHO) to detect psychoactive substance use and related disorders in primary care settings. It has shown good reliability, feasibility and validity in international, multi-site studies (WHO ASSIST Working Group 2002; Humeniuk et al. 2008), and is useful for identifying

substance use in poly-substance abusers with varying degrees of psychopathology. Seven items are included to assess alcohol and other drug use across ten categories (ie. tobacco products; alcoholic beverages; cannabis; cocaine; amphetamine-type stimulants; inhalants, sedatives or sleeping pills; hallucinogens; opioids; and a general category entitled “other”, in which the participant is required to specify the substance used). Frequency of use is assessed for each substance, and responses scored accordingly. The ASSIST commences with a screening questionnaire to assess lifetime use of alcohol and other drugs (AOD). Individuals responding “no” to this question may then terminate the interview. For those responding “yes” to any of the substances included, the remainder of the questionnaire need only be completed in relation to those substances. Responses to questions 2 – 5 are scored on a five-point frequency scale, while questions 6 – 7 are scored on a three-point scale. Question 8 assesses a history of intravenous drug use. (A more complete description of the tool and its scoring can be found elsewhere – Newcombe et al. 2005). Total scores are then obtained for each substance by summing the individual scores for questions 2 – 7 (inclusive), with a higher score indicative of greater risk for substance-related health problems. Scores of 0 – 10 for alcohol and 0 – 3 for illicit drugs were used to indicate that a participant was at low risk for substance-related health problems from her current pattern of use; scores of 11 – 26 for alcohol and 4 – 26 for illicit drugs to indicate moderate risk; and scores > 26 to indicate that a participant was at high risk of experiencing severe problems as a result of her current pattern of use and was likely to be dependent (WHO 2010). Participants were also assigned continuous scores for this assessment tool.

Medical and reproductive risk

Maternal medical and reproductive health was assessed using items from a standardised questionnaire developed for the DCHS (*see Appendix 2 – Maternal Respiratory & Medical Enrollment Form, p 236-248*). Risk profiles were quantified based on a model previously described by Collins and colleagues (1993), who used a similar study population and prospective cohort design as in the DCHS; and on complementary work by Pagel and colleagues (1990) and Feldman and colleagues (2000). HIV, tuberculosis, asthma, diabetes mellitus,

hypertension, cardiovascular disease, hyperemesis gravidarum, urinary tract infections and pelvic inflammatory disease are maternal biomedical conditions that may affect infant outcomes and thus were included. Similarly, reproductive risk was ascertained using an assessment of parity, prior intra-uterine death, prior delivery of a low birthweight infant, prior premature birth, prior caesarean section, poor maternal weight gain during the current pregnancy, current multiple gestation, and sex of the newborn. Further, maternal anthropometric measures taken antenatally and at regular postnatal intervals were included. Risk factors were scored as either present (1) or absent (0), and then summed to provide a continuous composite each for medical and for reproductive risk.

b) NEWBORN/INFANT ASSESSMENT

Anthropometry

All babies included in this study were born at Paarl Hospital. Trained clinical staff recorded weight, height and head circumference (HC) at birth and at infant age 6 months, and z-scores (standard deviation scores) were calculated. Low birthweight (LBW) was defined as less than 2,500g, according to the WHO parameters (WHO 2014). Low weight-for-age z-score (WAZ score) was defined as a score less than or equal to 2 standard deviations below the mean weight-for-age value (WHO 1995). Low head-circumference-for-age z-score (HCAZ score) was defined similarly. The z-score classification system is advantageous as it is sex-independent, employs a linear scale, and enables a comparison of results across age groups and indicators.

Gestational age

Gestational age was recorded from early ultrasound measurements done during the second trimester (preferred method); inferred from maternal fundal height at enrollment; or calculated from the self-reported date of last known menstrual period (Stein et al. 2015). Gestational age at delivery was then calculated in completed weeks of gestation, with infants categorised as small-for-gestational-age (SGA) or appropriate/large-for-gestational-age based on the revised Fenton preterm growth charts (Fenton & Kim 2013; Fenton et al. 2013). Prematurity was defined as birth before 37 completed weeks' gestation.

Developmental outcomes

Markers of infant development were assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) (Bayley 2006a). Scales were administered by two trained physiotherapists and one registered nurse, at infant age 6 months. All administrators had extensive experience in paediatric clinical and research settings, and underwent in-house training and piloting prior to formal data collection. A paediatric neurodevelopmental specialist visited sites regularly to ensure compliance with testing and standardised data collection, and completed protocols were checked randomly to ensure accuracy of scoring procedures. Individuals involved in Bayley-III administration were required periodically to complete an assessment under observation to ensure overall high-quality data collection.

The Bayley-III assesses infant and toddler development across five scales, namely, cognitive, language, motor, socio-emotional and adaptive behaviour. The language scale is subdivided further into receptive and expressive communication subtests; the motor scale into gross and fine motor subtests; and the adaptive behaviour scale into ten subtests, seven of which are applicable to infants younger than one year – communication, health and safety, leisure, self-care, self-direction, social and motor. The cognitive, language and motor assessments are conducted using items administered directly to the infant, while the socio-emotional and adaptive behaviour domains are assessed via a questionnaire completed by the primary caregiver. This assessment tool has been used widely in LMIC settings (eg. Ballot et al. 2012), and remains a key measure of developmental milestones.

The Bayley-III provides four types of norm-referenced developmental scores: scaled scores, composite scores, percentile ranks, and growth scores (Bayley 2006b). For our purposes, scaled scores were calculated from captured total raw scores on each subtest using the specialised software *Bayley-III Scoring Assistant Update Version 2.0.2 with Bayley-III PDA conduit (BayleyIII_PDA_2_0_2.exe)*. Scaled scores represent a child's performance on a subtest relative to his or her same-age peers and are sensitive to subtle differences in developmental outcomes (Bayley 2006c). They are scaled to a metric with a range of 1 to 19, a mean of 10 and a standard deviation (SD) of 3. According to the standard guidelines (Bayley 2006a,b,c), infants

scoring ≥ 1 SDs below the mean (ie. ≤ 7) in at least one subtest were classified as manifesting a clinically significant developmental effect. This cut-off threshold was selected as children with performance falling below it are likely to have a clinically significant deficit in that area of development. Dichotomous variables were used to demonstrate frequency distributions, while continuous variables were utilised in subsequent analyses.

2.5 Ethical considerations

The DCHS has been approved by the human research ethics committees of the Faculties of Health Sciences, University of Cape Town (UCT) (HREC REF: 401/2009) and Stellenbosch University (N12/02/0002) in South Africa; as well as by the Western Cape Department of Health (DoH) Provincial Research Committee (2011RP45), endorsing all research activities carried out at clinics and hospitals in the Drakenstein sub-district. All on-site female fieldworkers had at least a Grade 12 school certificate, prior experience in collaborative psychiatric/psychological research and were fluent either in English and Afrikaans; or in English and isiXhosa. Thus, they were able to administer questionnaires in the participants' preferred language. Further, fieldworkers received extensive in-service training on all aspects of Good Clinical Practice (GCP) (WHO 2002) prior to the commencement of data collection for the DCHS.

a) INFORMED CONSENT PROCESS

All participants were provided with a consent form describing the scope and aims of this study. Consent forms were provided in the participants' home language, namely, English, Afrikaans or isiXhosa. Only those who gave informed consent were included in the study. Individuals who chose not to participate in the study were reassured that their decision would not bias them or be held against them at any future juncture. Participants could also choose not to answer certain questions and still remain in the study, as long as exposure and diagnostic status could be determined reasonably. They could also take breaks, if requested, to lighten the interview burden; and were free to terminate or reschedule the interview should the need arise. Refreshments (water, fruit juice and biscuits) were provided to alleviate participant fatigue during the assessment sessions.

b) PRIVACY AND CONFIDENTIALITY

As participants were asked to divulge sensitive and potentially distressing information, a private consultation room was provided at each study site, and every effort was made by study staff to ensure a safe, confidential and supportive environment. Completed forms were stored in a locked filing system at the study sites and/or with the data management team. Although specific identifying data (such as full name and date of birth) were collected for tracking and study surveillance, all participants were given a unique identification (ID) number. Thus, clinical data and DNA were coded without personal identifiers. Clinical (ie. all non-genetic) information was maintained in a secure, password-protected web-based system designed by UCT, with strict rules of governance. All questionnaires were anonymous and the web-based system was de-identified.

c) REIMBURSEMENT FOR PARTICIPATION

Each participant was compensated with R50.00 per study visit for her time and effort, which is typical for similar South African studies.

The next chapter (based on *Publication 1*) will address the first research objective of this thesis, and will delineate risk factors for psychological trauma and PTSD in the Drakenstein cohort; as well as associations with adverse birth outcomes.

CHAPTER 3

PUBLICATION 1

Psychological trauma and posttraumatic stress disorder: an exploratory investigation of risk factors and associations with birth outcomes in the Drakenstein Child Health Study

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Synopsis

This chapter, assessing the variables which may confer increased risk for psychological trauma and PTSD in the DCHS cohort, as well as the association between trauma or PTSD and poor infant anthropometry at birth, will address Research Objective 1 of this thesis (*see Chapter 1, Section 1.6 – Study objectives and related publications, p 5*):

To investigate risk factors for maternal trauma and PTSD, and their association with adverse birth outcomes, in a cohort of mother-infant dyads in the Drakenstein sub-district, Western Cape.

This manuscript on which this chapter is based was submitted to a special issue of the *European Journal of Psychotraumatology (EJPT)*, focusing on trauma and adversity among populations in transition, and is currently under review.

Abstract

Background

Prenatal and peripartum trauma may be associated with poor maternal-foetal outcomes. However, relatively few data on these associations exist from LMIC countries, and populations in transition. We investigated the prevalence of and risk factors for maternal trauma and PTSD, and their association with adverse birth outcomes in the DCHS, a multidisciplinary birth cohort investigation of the influence of a number of antecedent risk factors on maternal and infant health outcomes over time.

Methods

Trauma exposure and PTSD were assessed using diagnostic interviews; validated self-report questionnaires measured other psychosocial characteristics. Gestational age at delivery was calculated and birth outcomes assessed by trained staff. Multiple logistic regression explored risk factors for trauma and PTSD; while associations with birth outcomes were investigated

using linear regression. Potential confounders included study site, SES, depression and smoking or alcohol use.

Results

544 mother-infant dyads were included. Lifetime trauma was reported in approximately two thirds of mothers, with about a third exposed to past-year IPV. The prevalence of current/lifetime PTSD was 19%. In multiple logistic regression, recent life stressors were significantly associated with lifetime trauma, when controlling for SES, study site and recent IPV. Childhood trauma and recent stressors were significantly associated with PTSD, controlling for SES and study site. While no association was observed between maternal PTSD and birth outcomes, maternal trauma was significantly associated with a 0.3 unit reduction (95% CI: 0.1; 0.5) in infant head-circumference-for-age z-scores (HCAZ scores) at birth in crude analysis, which remained significant when adjusted for study site and recent stressors in a multivariate regression model.

Conclusions

In this exploratory study, maternal trauma and PTSD were found to be highly prevalent; and our findings provide preliminary evidence suggesting that trauma may affect foetal growth adversely, as measured by birth head circumference. However, these findings are limited by a number of methodological weaknesses, and further studies are required to extend findings and to delineate causal links, mechanisms of association, and interventions to optimise maternal and child health.

Keywords: Trauma, PTSD, pregnancy, intergenerational, birth cohort, birth outcomes, South Africa

3.1 Introduction

Exposure to psychological trauma is highly prevalent in South Africa. According to nationally representative data from studies such as the SASH, most individuals experience at least one traumatic event in their lifetimes, including criminal victimisation, witnessing atrocities and IPV (Williams et al. 2004; 2007). PTSD is a debilitating stress-related psychiatric disorder affecting vulnerable individuals after traumatic exposure (APA 2013). A focus on PTSD is particularly relevant in LMIC settings such as South Africa, given the high trauma burden and additive risk factor profile in this context.

Findings from the National Comorbidity Survey (Kessler et al. 1995, 2005), a nationally representative study of 5,877 adults in the United States, indicated that women were overall more than twice as likely as men to develop lifetime PTSD (10.4% vs 5.0% prevalence, respectively). Pregnant women and new mothers, in particular, comprise a highly vulnerable subgroup (eg. Beck et al. 2011; Zaers et al. 2008; Söderquist et al. 2009). Prenatal trauma may place mothers at high risk of developing PTSD, and may result in a number of adverse maternal and foetal *sequelae*. For example, in their prospective cohort study of 839 nulliparas in Michigan, USA, Seng and colleagues (2011) reported that infants born to women who had experienced PTSD during pregnancy had a mean birthweight 283g less than those who had not developed PTSD following trauma exposure. Further, even the resilient (trauma-exposed) women were found to deliver infants with a mean birthweight 221g less than that of the non-traumatised group. PTSD was also found to be associated with shorter gestation in this cohort. Adverse birth outcomes such as these are important risk factors for poor growth and neurodevelopment in infancy and childhood.

South Africa provides a unique context for further work in the field of psychological trauma exposure and consequent PTSD. First, most individuals experience multiple traumatic events across their lifespan. Second, gender- and pregnancy-specific trauma is rife, and is likely to exert a range of adverse intergenerational effects. Third, ours is a population in transition. Despite a decline in recent years, the rate of urbanisation and of urban population growth in Sub-Saharan Africa remains among the highest worldwide (Tacoli et al. 2015). Further, the

number of lifetime immigrants in South Africa increased from approximately 800,000 pre-2001, to almost 1.5 million between 2001 and 2011 (Statistics SA 2014). The Western Cape was found to have the second highest provincial net-migration rate during this period. Female migrants in particular may be at increased risk of gender-specific trauma such as violence, inadequate access to basic infrastructure and the burden of unpaid, unsupported care work. Finally, despite the high burden of trauma and subsequent effects, there remains a relative dearth of data in this field from LMIC populations in transition, such as ours. Thus, the current study sought to investigate the prevalence of and risk factors for trauma and PTSD in a South African birth cohort study; and to explore associations with infant birth outcomes.

3.2 Methods

This study reports data from the DCHS – see *Chapter 2 – General Methodology (p 9-21)*. The analysis includes a sub-sample of mothers enrolled into the cohort between March 2012 and October 2014.

Details of participant enrollment can be found in *Chapter 2, Section 2.3 – Participant recruitment and follow-up (p 9-10)*; and ethical processes relevant to this study in *Chapter 2, Section 2.5 – Ethical considerations (p 20-21)*.

3.2.1 Measures

All assessment tools have been described in detail in *Chapter 2, Section 2.4 – Measures and variable calculation (p 10-20)*.

For the purposes of this analysis, data pertaining to specific variables were collected as follows:

Maternal assessment

- a) Sociodemographic characteristics** – using the SES questionnaire designed for the DCHS.
- b) Psychosocial risk factors** – using the World Mental Health Life Events Questionnaire (adapted from Myer et al. 2008), the Beck Depression Inventory (BDI-II) (Beck et al. 1961, 1988, 1996a,b), the Edinburgh Postnatal Depression Rating Scale (EPDS) (Cox et al.

1987), the SRQ-20 (Harding et al. 1980; Scholte et al. 2011) and the WHO's Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (WHO ASSIST Working Group 2002).

- c) Trauma exposure and PTSD** – using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1994), the Intimate Partner Violence (IPV) Questionnaire (adapted from Jewkes 2002; Shamu et al. 2011), and the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al. 1997; Sheehan et al. 1997, 1998).

Those women with a suspected high burden of psychiatric symptoms or stressors were referred to local routine service providers according to a structured standard operating procedure designed for the purposes of this study. In summary, participants with suspected psychopathology (as defined by the assessment tools) were detected on-site by trained fieldworkers, and ultimately referred to the study medical officer (MO). Following a psychiatric interview and risk assessment, the MO would then facilitate the most appropriate course of action for individual participants, including referral to emergency psychiatric services in Paarl. Further, educational pamphlets designed by the study team were made available to all participants. These pamphlets included information on common mental health disorders, as well as contact details for freely accessible resources in the Drakenstein sub-district.

Birth outcomes

Anthropometric variables (weight, height and head circumference) at birth were measured by clinical staff at Paarl Hospital and z-scores and gestational age calculated as described in *Chapter 2, Section 2.4 – Measures and variable calculation (p 18)*.

For our purposes, most birth outcomes of interest (ie. birthweight, WAZ scores, head-circumference-for-age and HCAZ scores) were expressed as both dichotomous and continuous variables, while SGA and preterm delivery were dichotomised. The present analysis was restricted to live births only.

3.2.2 Statistical analyses

All data were analysed using *Stata 12* (StataCorp Inc, College Station, Texas, USA). Frequency distributions and medians (interquartile ranges) were used to describe sociodemographic variables of interest (age, marital status, income); childhood and adult trauma exposure and stressful life events; PTSD, depression and psychological distress; alcohol and substance use; and birth anthropometry/gestation. Variables significantly associated with lifetime maternal trauma exposure; and, among trauma-exposed participants, with lifetime PTSD, were identified using χ^2 tests for categorical variables and Wilcoxon rank sum tests (Mann-Whitney tests) for non-normally distributed continuous variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to determine the strength of these associations. The associations between PTSD, potential confounders, birth anthropometric outcomes (WAZ, HCAZ, SGA) and gestational age at delivery were then explored. The selection of relevant covariates was informed by model building based on directed acyclic graphs which were generated prior to conducting the analyses. This was in order to differentiate between potential confounders versus mediating variables. Variables significantly associated each with trauma exposure and with PTSD in bivariate analysis (at $p < 0.05$) were included in regression models to examine independent predictors of decreased WAZ, decreased HCAZ, SGA, and shortened gestational age at delivery, respectively. Likelihood ratio tests were used to assess model fit.

3.3 Results

3.3.1 Maternal sociodemographic characteristics

Between March 2012 and October 2014, 1,047 mothers were enrolled in the DCHS. Those who had not yet given birth, and who had not yet completed the relevant ante- and postnatal assessments were excluded from the present analysis. Data from an additional fourteen women who had experienced antenatal losses or stillbirths during this time were also omitted. Thus, data from 544 mothers and 546 infants (including two sets of twins) were included in the final analysis.

Women had a median age of 26 years (interquartile range [IQR]: 21.9; 31.3), with most (62%) being unmarried, **Table 3.1**. Although most women (89%) had received some high school education (Grades 8 – 12), the vast majority (80%) was unemployed. While the overall SES of this study sample was low (87% reported a household income \leq R5,000 per month), a site-specific disparity was evident. Almost 50% of participants at Mbekweni reported an average household income of less than R1,000 per month, versus 35% at TC Newman. Notably, almost a third (32%) of the study sample reported being born outside of the Western Cape, while more than half (55%) at Mbekweni reported this. Almost half (49%) of the study sample reported living in an urban setting, with 44% living in a township and only a minority (7%) residing in a rural area. Approximately 20% of mothers were HIV infected.

3.3.2 Psychosocial risk factors

While the median (IQR) score for the measure of exposure to stressful life events in the past 12 months was 1 (0; 3), psychological distress (as assessed by the SRQ-20) was reported in 20% of participants, and approximately a quarter was found to score above threshold on measures of depression (BDI-II: 22%, EPDS: 27%), **Table 3.1**. Lifetime tobacco use was reported in a third of participants, with approximately 20% reporting smoking cigarettes during pregnancy. While approximately a third of the sample also reported lifetime alcohol use, only 3% self-reported antenatal use. It is noteworthy that a site-specific difference was found across a number of psychosocial parameters. For example, 69% of participants at TC Newman reported lifetime

tobacco use, compared to only 5% at Mbekweni; while 46% smoked cigarettes during pregnancy (versus 2% at Mbekweni). Similarly, 66% at TC Newman reported lifetime alcohol consumption, and 6% antenatal consumption; while only 10% and 1% reported lifetime and prenatal use, respectively, at Mbekweni, **Table 3.1**.

Table 3.1 Maternal sociodemographic and psychosocial characteristics

Variable	Mbekweni <i>n</i> (%)	TC Newman <i>n</i> (%)	Total <i>n</i> (%)
Number of mothers	309 (57)	235 (43)	544
Visit timepoint of MINI interview			
ANC2	100 (32)	76 (32)	176 (32)
6-10 weeks	9 (3)	14 (6)	23 (4)
6 months	182 (59)	119 (51)	301 (55)
18 months	18 (6)	26 (11)	44 (8)
Sociodemographic characteristics			
Ethnicity			
Black/African	305 (99)	1 (0.4)	306 (56)
Mixed-Race	4 (1)	232 (99)	236 (43)
Other	0 (0)	2 (0.9)	2 (0.4)
Migration			
Born in the Western Cape	140 (45)	228 (97)	368 (68)
Born outside of the Western Cape	169 (55)	7 (3)	176 (32)
Area of dwelling			
Urban	40 (13)	225 (96)	265 (49)
Rural	32 (10)	8 (3)	40 (7)
Township	237 (77)	2 (0.9)	239 (44)
Age at enrollment – median [IQR]	26.8 [22.1; 32.3]	25.0 [21.6; 29.7]	25.8 [21.9; 31.3]
Married/cohabiting	107 (35)	101 (43)	208 (38)
Educational achievement			
Primary	35 (11)	25 (11)	60 (11)
Some secondary	167 (54)	126 (54)	293 (54)
Completed secondary/any tertiary	107 (35)	84 (36)	191 (35)
Employed	61 (20)	49 (21)	110 (20)
Average household income			
< R1000/month	150 (49)	83 (35)	233 (43)
R1000-R5000/month	125 (40)	114 (49)	239 (44)
> R5000/month	34 (11)	38 (16)	72 (13)
SES quartile			
Lowest SES	110 (36)	56 (24)	166 (31)
Low-moderate SES	80 (26)	59 (25)	139 (26)
Moderate-high SES	70 (23)	61 (26)	131 (24)
Highest SES	49 (16)	59 (25)	108 (20)

Psychosocial risk factors

HIV-infected	113 (37)	8 (3)	121 (22)
Median recent life events [IQR]	1 [0; 2]	2 [1; 4]	1 [0; 3]
Lifetime tobacco use	15 (5)	162 (69)	177 (33)
Antenatal tobacco use	6 (2)	110 (46)	113 (21)
Lifetime alcohol use	31 (10)	156 (66)	187 (34)
Antenatal alcohol use	4 (1)	14 (6)	18 (3)
Depression – above threshold (BDI-II)	66 (21)	53 (23)	119 (22)
Depression – above threshold (EPDS)	80 (26)	65 (28)	145 (27)
Psychological distress – above threshold (SRQ-20)	52 (17)	56 (24)	108 (20)

3.3.3 Trauma exposure and PTSD – prevalence and risk factors

Approximately a third of the study sample reported a history of childhood trauma (34%) and of exposure to recent (past-year) IPV (32%), respectively, **Table 3.2**. Again, a notable site-specific difference was evident, with 43% of participants at TC Newman, versus 28% at Mbekweni having experienced childhood trauma; and 41% (TC Newman) versus 25% (Mbekweni) reporting past-year IPV exposure. Lifetime trauma exposure was reported in approximately two thirds (67%) of the sample. The prevalence of lifetime or recurrent PTSD (within the total sample) was 19%. Notably, participants with PTSD were significantly more likely to meet diagnostic criteria for a major depressive disorder (OR: 6.7; 95% CI: 4.1; 11.1); suicidality (OR 3.4; 95% CI: 2.1; 5.5); and alcohol dependence (OR 2.2; 95% CI: 1.0; 4.8).

Table 3.2 Maternal trauma exposure and PTSD

Variable	Mbekweni n (%)	TC Newman n (%)	Total n (%)
Childhood trauma – above threshold	86 (28)	101 (43)	187 (34)
Recent IPV – above threshold	77 (25)	96 (41)	173 (32)
Lifetime trauma exposure	202 (65)	164 (70)	366 (67)
Lifetime or recurrent PTSD	58 (19)	48 (20)	106 (19)

Crude analyses yielded significant associations each between recent IPV exposure, psychological distress, and recent stressful life events; and resultant trauma exposure in this study sample. In a multiple logistic regression model, recent stressful life events remained significantly associated with trauma, when controlling for SES, study site and recent IPV, **Table 3.3**.

In a second crude analysis restricted to trauma-exposed participants only (n = 366), PTSD was significantly more likely to occur among participants reporting lower levels of education, childhood trauma, recent stressful life events, depression (above threshold on the BDI-II and EPDS) and psychological distress, **Table 3.4**. In a multiple logistic regression model restricted to this traumatised sub-sample, childhood trauma and recent stressful life events remained significantly associated with PTSD, when controlling for SES and study site.

3.3.4 Infant birth outcomes

Fifteen percent of infants in the study sample were born preterm. The median (IQR) birthweight was 3,080 (2,730; 3,420) g, and the median (IQR) head circumference at birth was 34 (33; 35) cm. On average, infants had a median (IQR) WAZ of -0.5 (-1.3; 0.1) and a median HCAZ of -0.5 (-1.2, 0.2), **Table 3.5**. Notable site-specific differences were also observed across certain birth outcomes. For example, the median (IQR) birthweight for infants at TC Newman (2,960 (2,610; 3,350) g) was lower than at Mbekweni (3,170 (2,830; 3,440) g). Further, when dichotomising birth outcomes, it was found that the prevalence of LBW at TC Newman (19%) was higher than at Mbekweni (11%). Similarly, there were differences in dichotomised WAZ and HCAZ scores, with the prevalence of low WAZ and HCAZ at TC Newman (11% and 12% respectively) higher than at Mbekweni (6% and 8%). A higher proportion of infants was also born SGA at TC Newman (31%) than at Mbekweni (22%).

Table 3.3 Variables associated with lifetime trauma exposure (*n* = 544)

Variable	No trauma exposure <i>n</i> (%)	Trauma exposure <i>n</i> (%)	Unadjusted odds ratio [95% CI]	<i>P</i> -value	Adjusted odds ratio [95% CI]	<i>P</i> -value
Recruitment site						
Mbekweni	107 (35)	202 (65)	Reference		Reference	
TC Newman	71 (30)	164 (70)	1.2 [0.9; 1.8]	0.277	1.0 [0.7; 1.5]	0.974
SES quartile						
Highest SES	36 (33)	72 (67)	Reference		Reference	
Moderate-high SES	43 (33)	88 (67)	1.0 [0.6; 1.8]	0.934	1.0 [0.6; 1.8]	0.951
Low-moderate SES	48 (35)	91 (65)	0.9 [0.6; 1.6]	0.844	0.9 [0.5; 1.5]	0.666
Lowest SES	51 (31)	115 (69)	1.1 [0.7; 1.9]	0.650	1.1 [0.7; 1.9]	0.642
Recent IPV exposure						
Below threshold	133 (36)	238 (64)	Reference		Reference	
Above threshold	45 (26)	128 (74)	1.6 [1.1; 2.4]	0.023	1.4 [0.9; 2.1]	0.107
Median recent stressful life events [IQR]	1 [0; 2]	1 [0; 3]	1.2 [1.1; 1.3]	0.002	1.2 [1.0; 1.3]	0.008
Psychological distress (SRQ-20)						
Below threshold	159 (36)	277 (64)				
Above threshold	19 (18)	89 (82)	2.7 [1.6; 4.6]	< 0.001		

Table 3.4 Variables associated with lifetime/recurrent PTSD among trauma-exposed participants (*n* = 366)

Variable	No PTSD <i>n</i> (%)	PTSD <i>n</i> (%)	Unadjusted odds ratio [95% CI]	<i>P</i> -value	Adjusted odds ratio [95% CI]	<i>P</i> -value
Recruitment site						
Mbekweni	144 (71)	58 (29)	Reference		Reference	
TC Newman	116 (71)	48 (29)	1.0 [0.7; 1.6]	0.907	0.7 [0.4; 1.1]	0.113
SES quartile						
Highest SES	54 (75)	18 (25)	Reference		Reference	
Moderate-high SES	60 (68)	28 (32)	1.4 [0.7; 2.8]	0.344	1.4 [0.7; 2.9]	0.349
Low-moderate SES	56 (62)	35 (38)	1.9 [0.9; 3.7]	0.070	1.6 [0.8; 3.2]	0.183
Lowest SES	90 (78)	25 (22)	0.8 [0.4; 1.7]	0.606	0.7 [0.3; 1.5]	0.354
Education						
Completed secondary/any tertiary	87 (72)	34 (28)	Reference			
Some secondary	153 (74)	54 (26)	0.9 [0.5; 1.5]	0.692		
Primary	20 (53)	18 (47)	2.3 [1.1; 4.9]	0.029		

Childhood trauma						
Below threshold	175 (76)	56 (24)	Reference		Reference	
Above threshold	85 (63)	50 (37)	1.8 [1.2; 2.9]	0.010	1.8 [1.1; 2.9]	0.029
Median recent stressful life events [IQR]	1 [0, 3]	2 [0, 4]	1.2 [1.1; 1.3]	0.002	1.2 [1.0; 1.3]	0.008
Depression (BDI-II)						
Below threshold	207 (74)	73 (26)	Reference			
Above threshold	53 (62)	33 (38)	1.8 [1.1; 2.9]	0.029		
Depression (EPDS)						
Below threshold	197 (74)	68 (26)	Reference			
Above threshold	63 (62)	38 (38)	1.7 [1.1; 2.8]	0.025		
Psychological distress (SRQ-20)						
Below threshold	212 (77)	65 (23)	Reference			
Above threshold	48 (54)	41 (46)	2.8 [1.7; 4.6]	<0.001		

Table 3.5 Infant birth outcomes

Variable	Mbekweni <i>n</i> (%)	TC Newman <i>n</i> (%)	Total <i>n</i> (%)
Number of infants; sets of twins	311 (57); 2	235 (43); 0	546
Female	163 (52)	107 (46)	270 (49)
Median gestation at delivery [IQR]	39 [38; 40]	39 [38; 40]	39 [38; 40]
Preterm birth (< 37 weeks)	51 (16)	32 (14)	83 (15)
Median weight in grams [IQR]	3170 [2830; 3440]	2960 [2610; 3350]	3080 [2730; 3420]
Low birthweight (< 2500g)	34 (11)	45 (19)	79 (14)
Median WAZ ¹ [IQR]	-0.4 [-1.2; 0.3]	-0.8 [-1.5; -0.1]	-0.5 [-1.3; 0.1]
Low WAZ (WAZ of -2 or below)	19 (6)	27 (11)	46 (8)
SGA	67 (22)	74 (31)	141 (26)
Median head circumference in cm [IQR]	34 [33; 35]	34 [32; 34]	34 [33; 35]
Median HCAZ ² [IQR]	-0.3 [-1.1; 0.4]	-0.6 [-1.3; 0.1]	-0.5 [-1.2; 0.2]
Low HCAZ (HCAZ of -2 or below)	25 (8)	28 (12)	53 (10)

¹Weight-for-age z-score; ²Head-circumference-for-age z-score

3.3.5 Association between maternal trauma, PTSD and infant birth outcomes

No association was observed between maternal PTSD and any of the birth outcomes in this study (ie. decreased WAZ score, decreased HCAZ score, SGA and preterm delivery). However, crude analyses of the association between trauma exposure and adverse birth outcomes revealed that maternal trauma was significantly associated with a 0.3 unit reduction in infant HCAZ scores at birth (95% CI: 0.1; 0.5), **Table 3.6**. This association remained significant when adjusted for study site, SES and recent life stressors (*Table 3.6, adjusted model A*) in a multivariate regression model; and tended towards significance when additionally adjusted for WAZ score at birth (*Table 3.6, adjusted model B*). Antenatal alcohol use and smoking were not included in the final regression models due to temporality. In this analysis, both trauma exposure and PTSD were assessed over the course of the participants' lifetimes. However, data on alcohol use and smoking were derived only from the antenatal maternal assessment. Thus, it is likely that these variables acted as mediators, rather than confounders, in the relationship each between trauma, PTSD and adverse birth outcomes.

Table 3.6 Association between lifetime trauma exposure and infant HCAZ¹ at birth, with and without adjustment for infant WAZ² at birth

Variable	Median HCAZ [IQR]	Unadjusted regression coefficient [95% CI]	P-value	(A) Model without adjustment for WAZ: Regression coefficient [95% CI]	P-value	(B) Model with adjustment for WAZ: Regression coefficient [95% CI]	P-value
Recruitment site							
Mbekweni	-0.3 [-1.1; 0.4]	Reference		Reference		Reference	
TC Newman	-0.6 [-1.3; 0.1]	-0.3 [-0.6; -0.1]	< 0.001	-0.3 [-0.5; -0.1]	0.013	-0.02 [-0.2; 0.2]	0.780
SES quartile							
Highest SES	-0.3 (-1.0; 0.2)	Reference		Reference		Reference	
Moderate-high SES	-0.5 [-1.3; 0.1]	-0.2 [-0.5; 0.1]	0.173	-0.2 [-0.5; 0.1]	0.127	-0.04 [-0.3; 0.2]	0.755
Low-moderate SES	-0.5 [-1.5; 0.3]	-0.2 [-0.5; 0.1]	0.241	-0.2 [-0.5; 0.1]	0.195	-0.005 [-0.2; 0.2]	0.970
Lowest SES	-0.4 [-1.2; 0.3]	-0.04 [-0.3; 0.3]	0.799	-0.1 [-0.4; 0.2]	0.516	0.1 [-0.1; 0.4]	0.347
Antenatal tobacco use							
Below threshold	-0.4 [-1.2; 0.4]	Reference					
Above threshold	-0.6 [-1.3; 0.1]	-0.3 [-0.6; -0.1]	0.017				
Antenatal alcohol use							
Below threshold	-0.4 [-1.2; 0.3]	Reference					
Above threshold	-1.3 [-1.8; -0.6]	-0.9 [-1.4; -0.3]	0.002				
IPV exposure							
No recent IPV	-0.3 [-1.2; 0.4]	Reference					
Any recent IPV	-0.6 [-1.3; 0.1]	-0.3 [-0.5; -0.1]	0.006				
Recent life events		-0.1 [-0.1; -0.03]	0.001	-0.1 [-0.1; -0.0003]	0.049	-0.03 [-0.1; 0.01]	0.150
Infant WAZ		0.7 [0.6; 0.8]	< 0.001			0.7 [0.6; 0.8]	< 0.001
Trauma exposure							
No exposure	-0.2 [-1.2; 0.5]	Reference		Reference		Reference	
Trauma exposure	-0.6 [-1.3; 0.1]	-0.3 [-0.5; -0.1]	0.009	-0.2 [-0.5; -0.03]	0.026	-0.2 [-0.3; 0.03]	0.054

¹Head-circumference-for-age z-score; ²Weight-for-age z-score

3.4 Discussion and conclusions

The key findings of this exploratory investigation of maternal psychological trauma, PTSD and associated birth outcomes were (1) the majority of women had experienced at least one lifetime traumatic event, including childhood abuse and/or IPV, with a notable prevalence of PTSD; (2) childhood trauma and recent stressful life events were each significantly associated with PTSD, when controlling for SES and study site; (3) although infant anthropometric markers at birth were within the WHO “normal” range, there was a notable site-specific difference across a number of parameters, with infants born to mothers from TC Newman fairing more poorly overall; (4) while no associations were observed between PTSD and subsequent birth outcomes, maternal psychological trauma was found to be significantly associated with a reduction in HCAZ scores at birth, when controlling for a number of potentially confounding variables.

The high trauma burden in our study sample is largely in line with the local and international literature. For example, while the National Comorbidity Survey (NCS) reported that approximately 60% of men and 50% of women had been exposed to at least one traumatic event (Kessler et al. 1995), findings from the SASH indicated that nearly 75% of South Africans experienced some trauma during their lifetimes (Williams et al. 2007). It is noteworthy, however, that the prevalence of PTSD in our sample (19%) was far higher than has been reported previously (eg. Herman et al. 2009; Kessler et al. 1995). This may be due to a number of interrelated factors. First, ours is a particularly at-risk population, with the prevalence of depression and substance use notably higher than those in the SASH (Herman et al. 2009). Both factors may predispose individuals to the development of PTSD following trauma exposure. Second, our study sample comprises only women, of reproductive age. PTSD exhibits a significant gender-bias, which may be related to environmental or neurobiological factors. Third, the high level of internal migration and urban transition found in our study sample imposes an additive risk. In addition to socioeconomic inequity, exposure to xenophobic behaviours (eg. Harris 2002), employment instability, and exclusion from

citizenship rights may place additional stress on migrant households and individuals (Tacoli et al. 2015).

Childhood trauma and stressful life events each were found to be significantly associated with the development of PTSD. The role of early negative life events in precipitating or exacerbating psychological disorders in adulthood has been well-documented (eg. Yehuda et al. 2001b). For example, in her study of 1,196 victims of substantiated child abuse and neglect from 1967 to 1971 in a Midwestern metropolitan county area, USA, Widom (1999) reported that childhood victimisation was associated with an increased risk of lifetime and current PTSD, with 37.5% of the victims of childhood sexual abuse, 32.7% of those physically abused, and 30.6% of the victims of childhood neglect meeting the DSM criteria for lifetime PTSD. This association may be underpinned by revictimisation of the survivors of childhood maltreatment (eg. Messman-Moore & Long 2003); as well as by neurobiological alterations such as hyperactive stress reactivity and exaggerated HPA-axis functioning (Heim et al. 2009). Further, in the two meta-analyses of the predictors of PTSD in adults (Brewin et al. 2000; Ozer et al. 2003 – see *Chapter 1, Section 1.2 - Environmental and genetic risk factors for psychological trauma and PTSD, p 2*), it was found that prior trauma and additional life stress each significantly increased the risk of developing this disorder.

In our sample, measures of infant anthropometry at birth were found to be within the normal range according to the WHO child growth standards (WHO 2014). This may be accounted for by the relatively high level of education amongst our maternal study population, as well as by the perinatal care and health promotion inherent in a longitudinal study such as ours.

However, the site-specific difference in birth anthropometry (with poorer outcomes at TC Newman) may be attributable to the discordant risk factor profile between the two sites (see also *Chapter 4 – Publication 2, p 66-67*). For example, the prevalence of maternal lifetime and prenatal tobacco or alcohol use, as well as of childhood trauma and past-year IPV, all were found to be higher at TC Newman than at Mbekweni, which is in line with the poorer birth outcomes at TC Newman.

In contrast to a notable evidence base of the adverse effects of prenatal psychological trauma on birth outcomes, neither maternal trauma nor PTSD was significantly associated with a reduction in most anthropometric measures, or in a shortened gestational length in these data. In their recent systematic review of 49 peer-reviewed studies assessing the effect of disasters on pregnancy outcomes, maternal mental health and child development, Harville and colleagues (2010) concluded that a major concern for pregnant women exposed to disaster relates to decreased foetal growth, particularly in the most directly exposed women. Similarly, there is a large body of work documenting the association between maternal stress or distress, and outcomes such as low birthweight and preterm delivery. In their prospective, population-based study of 5,872 women with singleton pregnancies attending an antenatal care clinic in Denmark, Hedegaard and colleagues (1993) reported that – compared to low psychological distress – the relative risk of preterm delivery for moderate distress during late pregnancy was 1.22 (95% CI 0.84; 1.79), and for high distress was 1.75 (95% CI 1.20; 2.54). Further, there is evidence that maternal exposure to prenatal life event stress may be associated with a notable decrease in infant birthweight, independent of biomedical risk (Wadhwa et al. 1993). In their longitudinal cohort study of 1,100 pregnant women recruited from prenatal clinics in inner-city New Haven, Connecticut, Rogal and colleagues (2007) also reported that preterm delivery was nearly three times more likely in participants with PTSD, versus those without (OR = 2.72, 95% CI: 0.91, 8.14).

The discrepancy between our study findings and this compelling body of published work may be due to our limited power to detect smaller effect sizes; to our use of different assessment tools, each with measurement biases that may have reduced our ability to detect associations; to our LMIC study setting (in contrast to the high-income populations investigated in most prior work); or to the temporality of risk factors (eg. “recent”, or past-year trauma may have predated pregnancy). While we did not investigate associations of low infant birthweight in the current analysis, maternal trauma was found to be significantly associated with reduced head circumference z-scores (HCAZ) at birth in our final multivariate model. This is in line with one study (Engel et al. 2005) which found that women with posttraumatic stress symptomatology resulting from the World Trade Centre Attacks were more likely to deliver infants with reduced

head circumference at birth ($\beta=-0.07$, $SE=0.03$, $P=0.01$). It may also be seen as complementary to another prior study by our group, demonstrating that maternal depression is significantly associated with reduced HCAZ scores in the Drakenstein cohort, when adjusted for study site, SES, and recent stressful life events (Brittain et al. 2015). Taken together, these findings suggest that different maternal risk factors, measured by a range of assessment tools (each with unique biases) and acting through diverse mediators, may contribute to the heterogeneity of observed associations with infant birth outcomes in this vulnerable study population.

In fact, it is likely that a number of mediators underlie the association between maternal psychological trauma and reduced foetal head growth. From a neurobiological perspective, it is hypothesised widely that stress activates both the HPA axis and the sympathetic nervous system (SNS) (eg. Vermetten & Bremner 2002). Thus, elevated levels of corticotrophin releasing hormone (CRH), adrenocorticotropin hormone (ACTH) and cortisol – consistent with a hyperactive stress response – may contribute to foetal growth restriction, as has been documented (eg. Wadhwa et al. 2008; Challis et al. 2001). Further, abnormally elevated levels of adrenaline and noradrenaline (characteristic of SNS hyperactivation) may be associated with increased uterine artery resistance, likely mediated by sympathetic vasoconstriction (Teixeira et al. 1999). Intra-uterine growth restriction in turn may result from impaired transplacental blood flow (Bower et al. 1993).

Limitations of the current study include potential recall bias resulting from self-reported maternal data; and limited generalisability of findings due to the relative homogeneity of the study sample. While clinician-administered assessment tools (ie. the MINI) were employed to supplement self-reported findings, some of these assessments were completed at a timepoint after the index infants' birth, thus potentially complicating the temporality of the associations. Further, as this study was conducted in a peri-urban region of low SES, the study sample may not be generally representative of South Africa. Another limitation of the current study is the strong likelihood of unmeasured and residual confounding. For example, while we adjusted for the effect of study site and SES in our analysis, the standardised conceptualisation and accurate measurement of the latter variable remains highly challenging (Oakes & Rossi 2003; Ndhlovu &

Khalema 2015); and even good measures are likely to retain some residual confounding (Kaufman et al. 1997).

Despite its limitations, our study constitutes a novel exploratory investigation of the prevalence of and risk factors for psychological trauma and PTSD during pregnancy, as well as associated birth outcomes, in a LMIC population in transition. However, given the high prevalence of PTSD found in our sample; as well as the methodological shortcomings of the current study, there is a clear need for further research in settings such as ours, focused on the association between stressful life events, traumatic exposure, and consequent PTSD. Adequate detection and appropriate treatment of trauma-exposed individuals in the pre- and peripartum period would be helpful to curb the detrimental effects on mother and child. Further, longitudinal follow-up of maternal psychological risk, mother-child attachment and measures of developmental and child mental health will be important to evaluate the long-term functional effects of maternal trauma exposure. In future, further work in this field would be useful to extend our findings, to delineate causal pathways and neurobiological mechanisms, and to inform appropriate maternal and child health interventions.

In the next chapter – as per *Publication 2* – associations between maternal exposure to recent IPV and subsequent delivery of an infant with low birthweight will be explored, thereby addressing the second research objective of this thesis.

CHAPTER 4

PUBLICATION 2

Intimate partner violence: associations with low infant birthweight in the Drakenstein Child Health Study

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Synopsis

This publication, which investigates the burden of IPV in the DCHS maternal cohort, as well as its association with delivery of an infant with low birthweight (LBW), will address specifically Research Objective 2 of this thesis (*see Chapter 1, Section 1.6 – Study objectives and related publications, p 6*):

To determine the prevalence of maternal trauma exposure (including IPV), and its association with low infant birthweight in the study cohort.

This manuscript has been published in *Metabolic Brain Disease*, as follows:

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Abstract

Introduction

Violence against women is a global public health problem. Exposure to IPV during pregnancy has been associated with a number of adverse maternal and foetal outcomes, including delivery of a low birthweight (LBW) infant. However, there is a paucity of data from LMIC countries. We examined the association between antenatal IPV and subsequent LBW in the DCHS.

Methods

Antenatal trauma exposure was assessed using the Childhood Trauma Questionnaire (CTQ) and an IPV assessment tool specifically designed for the purposes of this study. Potential confounding variables including maternal sociodemographics, pregnancy intention, partner support, biomedical and mental illness, substance use and psychosocial risk, were also assessed. Bivariate and multiple regression analyses were performed to determine the

association between IPV during pregnancy and delivery of an infant with LBW and/or low weight-for-age z-scores (WAZ scores).

Results

The final study sample comprised 263 mother-infant dyads. In multiple regression analyses, the model run was significant [$r^2 = 0.14$ (adjusted $r^2 = 0.11$, $F(8, 212) = 4.16$, $p = 0.0001$]. Exposure to physical IPV occurring during the past year was found to be significantly associated with LBW [$t = -2.04$, $p = 0.0429$] when controlling for study site (clinic), maternal height, ethnicity, SES, substance use and childhood trauma. A significant association with decreased WAZ scores was not demonstrated.

Conclusions

Exposure of pregnant women to IPV may affect newborn health. Further research is needed in this field to assess the relevant underlying mechanisms, to inform public health policies and to develop appropriate trauma and IPV interventions for LMIC settings.

Keywords: Intimate partner violence; trauma; pregnancy; low birthweight; South Africa

4.1 Introduction

The prevalence of violence against women is exceedingly high in South Africa and globally (Devries et al. 2013). IPV may be defined as behaviour by an intimate partner that causes physical, sexual or psychological harm, including acts of physical aggression, sexual coercion, psychological abuse and controlling behaviours (WHO 2013a). In the WHO's Multi-Country Study on Women's Health and Domestic Violence against Women, García-Moreno and colleagues (2006) reported that the prevalence of lifetime physical and/or sexual IPV against women aged 15 – 49 (n = 24,097) across ten countries ranged between 15% and 71%. Between 4% and 54% of participants reported physical and/or sexual IPV in the past year.

A similar trend is evident in the South African context. According to a secondary analysis of data from the SASH, 31% of the study sub-sample (n = 1,229 married and cohabiting women) reported IPV exposure in their most recent intimate relationship (Gass et al. 2010). Further, in their study of female homicides, Abrahams and colleagues (2009) reported that 50% of all murders committed were by current or previous intimate partners. This translates to the highest reported intimate femicide rate globally – 8.8 per 100,000 women.

In Africa, women of reproductive age constitute a particularly vulnerable subgroup, with prevalence rates of IPV during pregnancy ranging between 2% and 57% (meta-analysis yielded an overall prevalence of 15%) (Shamu et al. 2011). These rates are among the highest worldwide. IPV during pregnancy is of great societal and public health concern, in part because it may be associated with a range of adverse maternal and foetal *sequelae*. Women exposed to IPV while pregnant may experience consequent physical and mental health outcomes including pregnancy loss, inadequate weight gain, depression and PTSD (Taillieu & Brownridge 2010; Martin et al. 2006; Rodriguez et al. 2008). Adverse infant outcomes may include preterm labor/delivery and low birthweight (LBW) (Taillieu & Brownridge 2010; Covington et al. 2001; Murphy et al. 2001).

LBW, in particular, is widespread and may be associated with a range of infant and childhood deficits (Aarnoudse-Moens et al. 2009; Harder et al. 2007). With a global LBW rate (LBWR) of

approximately 15.5% (ie. over 20 million babies born weighing less than 2,500g worldwide) (UNICEF & WHO 2004), the vast majority of these cases occurs in LMIC regions. In an early methodological assessment and meta-analysis of the determinants of LBW, Kramer (1987) reported three classes of risk factors, ie. unmodifiable factors with an established causal effect (eg. maternal reproductive history); factors with a casual effect that are modifiable in the short-term (eg. maternal nutrition, pre-pregnancy weight and substance use); and causal factors that are modifiable in the long-term (eg. maternal SES). Further, Kramer put forward that these factors exert their effect by increasing the risk for intra-uterine growth restriction (IUGR) and/or for shortened gestational duration, both of which are mechanisms of action for LBW. In high-income (HIC) countries, cigarette smoking was reported to be the major determinant of IUGR (and LBW), while poor gestational nutrition, decreased maternal anthropometry and maternal infection (malaria) were found to be most influential in LMIC regions. While pre-pregnancy weight, prior history of prematurity and cigarette smoke were reported to have well-established causal effects on decreased gestational duration, the majority of cases in HIC and LMIC countries was found to be unexplained.

In their recent systematic review and meta-analysis of studies conducted in HIC regions (United States, Norway and Australia), Murphy and colleagues (2001) investigated the association between IPV during pregnancy and low infant birthweight. These authors reported that women exposed to physical, sexual or emotional abuse during pregnancy were 1.4 times more likely to give birth to a newborn with LBW than those who were not abused (95% CI: 1.1; 1.8). There is some evidence that an association of similar strength may exist in LMIC countries. For example, in their survey of 110 pregnant women delivering at a public hospital in Mexico, Valdez-Santiago and Sanín-Aguirre (1996) found that those who had experienced IPV during pregnancy were approximately four times more likely to deliver LBW infants (95% CI: 1.3; 12.3), and that the average birthweight of newborns of abused women was 540g less ($p < 0.01$ adjusted by age and parity) when compared to those who had not experienced such violence. Similarly, in their study of 930 pregnant teenagers from a socioeconomically disadvantaged community in Sao Paulo, Brazil, Ferri and colleagues (2007) found that 21.9% of mothers reported a history of lifetime violence, with 2% having experienced IPV during pregnancy.

Further, it was found that violence during pregnancy was associated independently with LBW (prevalence ratio = 2.59, 95% CI: 1.05; 6.40).

Unfortunately, despite the high burden of IPV, data from LMIC regions such as South Africa remain relatively sparse. There is a need for further work in this area to delineate the association between this form of abuse and its many potential adverse outcomes. Contextual factors particularly relevant to LMIC settings, such as sociodemographic variables, childhood trauma and stress-related psychopathology, may confound this association and should also be considered. The purpose of this analysis was to determine whether there is an association between exposure to physical, emotional and/or sexual IPV during pregnancy and subsequent delivery of an infant with LBW in the context of a South African community setting, while controlling for a number of potential contextual confounders.

4.2 Methods

This study reported data from the DCHS. At the time of manuscript preparation, the DCHS was ongoing. Data collection had commenced in March 2012. Details of participant enrollment can be found in *Chapter 2, Section 2.3 – Participant recruitment and follow-up (p 9-10)*.

4.2.1 Measures

All assessment tools have been described in detail in *Chapter 2, Section 2.4 – Measures and variable calculation (p 10-20)*. For the purposes of this analysis, data pertaining to specific variables were collected as follows:

Maternal assessment

- a) **Sociodemographic characteristics and planning of birth/partner support**– using questionnaires developed specifically for the DCHS.
- b) **Stressful life events, trauma exposure and PTSD** – using the World Mental Health Life Events Questionnaire (Myer et al. 2008); the Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1994); the Intimate Partner Violence (IPV) Questionnaire (adapted from Jewkes 2002; Shamu et al. 2011); and the Modified Posttraumatic Stress Disorder Symptom Scale (MPSS) (Foa et al. 1993).
- c) **Psychological distress and depression** – using the SRQ-20 (Harding et al. 1980; Scholte et al. 2011); Beck Depression Inventory II (BDI-II) (Beck et al. 1961, 1988, 1996a,b); and the Edinburgh Postnatal Depression Rating Scale (EPDS) (Cox et al. 1987).
- d) **Substance use** – using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (WHO ASSIST Working Group 2002; Humeniuk et al. 2008).
- e) **Medical and reproductive risk** – using a standardised questionnaire developed for the DCHS (adapted from Pagel et al. 1990; Feldman et al. 2000).

Newborn outcomes

Newborn anthropometric variables (birthweight and WAZ score) were measured and calculated as described in *Chapter 2, Section 2.4 – Measures and variable calculations (p 18)*. For our purposes, both outcomes of interest (ie. LBW and low WAZ scores) were expressed as dichotomous and continuous variables.

4.2.2 Ethical considerations

Full details of ethical approval for these research activities may be found in *Chapter 2, Section 2.5 – Ethical considerations (p 20-21)*. This analysis was also approved by the institutional review board of the University of California, Los Angeles (UCLA).

Following written informed consent, those women who wished to participate were asked to complete a battery of measures described above. On-site female fieldworkers administering these measures were selected according to criteria previously found to affect women's willingness to divulge information about IPV exposure (Jansen et al. 2004), including multi-cultural and interpersonal rapport, empathy and non-judgmentalism, emotional maturity and sensitivity to the complex psychosocial issues relating to IPV. Those involved directly in IPV-related data collection underwent additional specialised training based on the WHO clinical and policy guidelines (WHO 2013a) and on the programme designed for the WHO Multi-Country Study on Women's Health and Domestic Violence (Jansen et al. 2004). This training included aspects of women-centred care and first-line support for those reporting IPV (eg. gender sensitivity and help in accessing resources and mobilising social support); as well as basic knowledge of IPV, including its causes, characteristics, impact and laws relevant to victims of abuse. Powerpoint presentations, instructional handouts and manuals, role-play sessions and directly observed interviews served as adjuncts to the basic training framework.

4.2.3 Sample size

At the time of this analysis, a total of 566 women had been enrolled in the larger DCHS. Of these, 113 had been lost to follow-up, refused to participate in this sub-study or had not

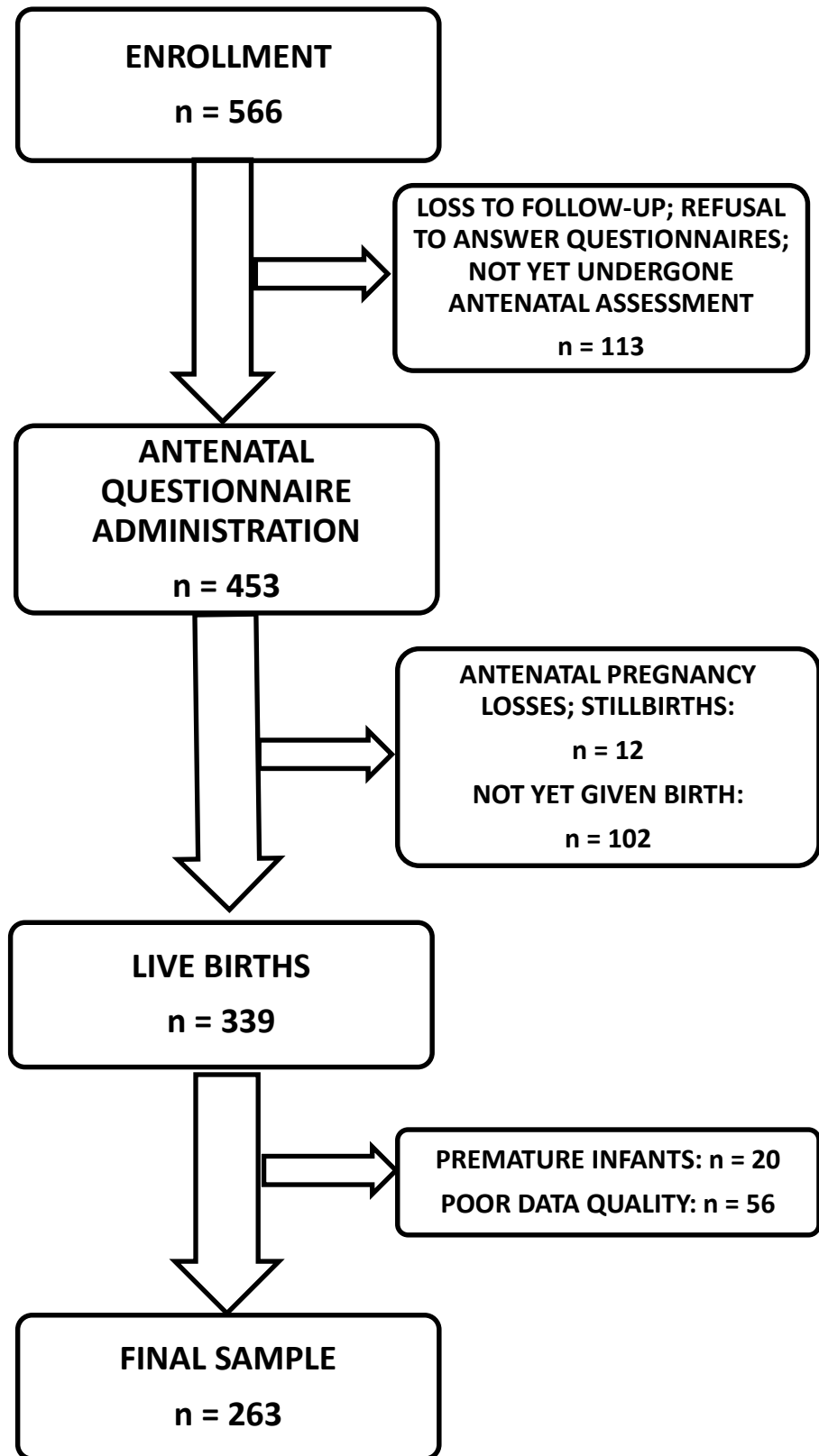
returned yet for questionnaire administration at the time of data collection. Thus, a total of 453 women completed the measures described above. Of this group, 12 experienced antenatal pregnancy losses or stillbirths. At the time of data collection, 339 study participants had delivered live infants. Live infants born prematurely (before 37 weeks' completed gestation (WHO 1995)) were excluded from this analysis (n = 20). Data from a further 56 participants were omitted due to problems with quality control. Most of these quality difficulties arose in the first few months of data collection, and pertained to incorrect or incomplete questionnaires, duplicated participant identification numbers, and erroneous data capturing. Human error was noted to decrease significantly as staff training and experience improved. The final sample for this analysis comprised 263 mother-infant dyads (see Figure 4.1).

4.2.4 Statistical analyses

Frequency distributions were used to describe sociodemographic characteristics of interest; psychosocial risk factors (including exposure to trauma); and adverse newborn outcomes (LBW and low WAZ scores). Bivariate correlation analyses (Pearson correlation coefficients) were then applied to determine the variables to be included in the regression models. These correlation analyses included potential confounding variables such as sociodemographics of the study population; maternal relationship with partner; psychosocial stressors and psychopathology; and medical/reproductive risk, based on prior literature (eg. Kramer 1987; Taillieu & Brownridge 2010), directed acyclic graphs and model building prior to the analyses. The interaction between maternal traumatic exposure (predictor) and low infant birthweight (outcome) was tested then in the final model using multiple linear regression analyses. Based on the results of the bivariate correlation analyses, two multiple regression models were generated:

- 1) To determine the association between past-year IPV exposure and LBW;
- 2) To determine the association between past-year IPV exposure and low WAZ score.

Figure 4.1 Participant enrollment and sample collection



4.3 Results

4.3.1 Maternal sociodemographic characteristics

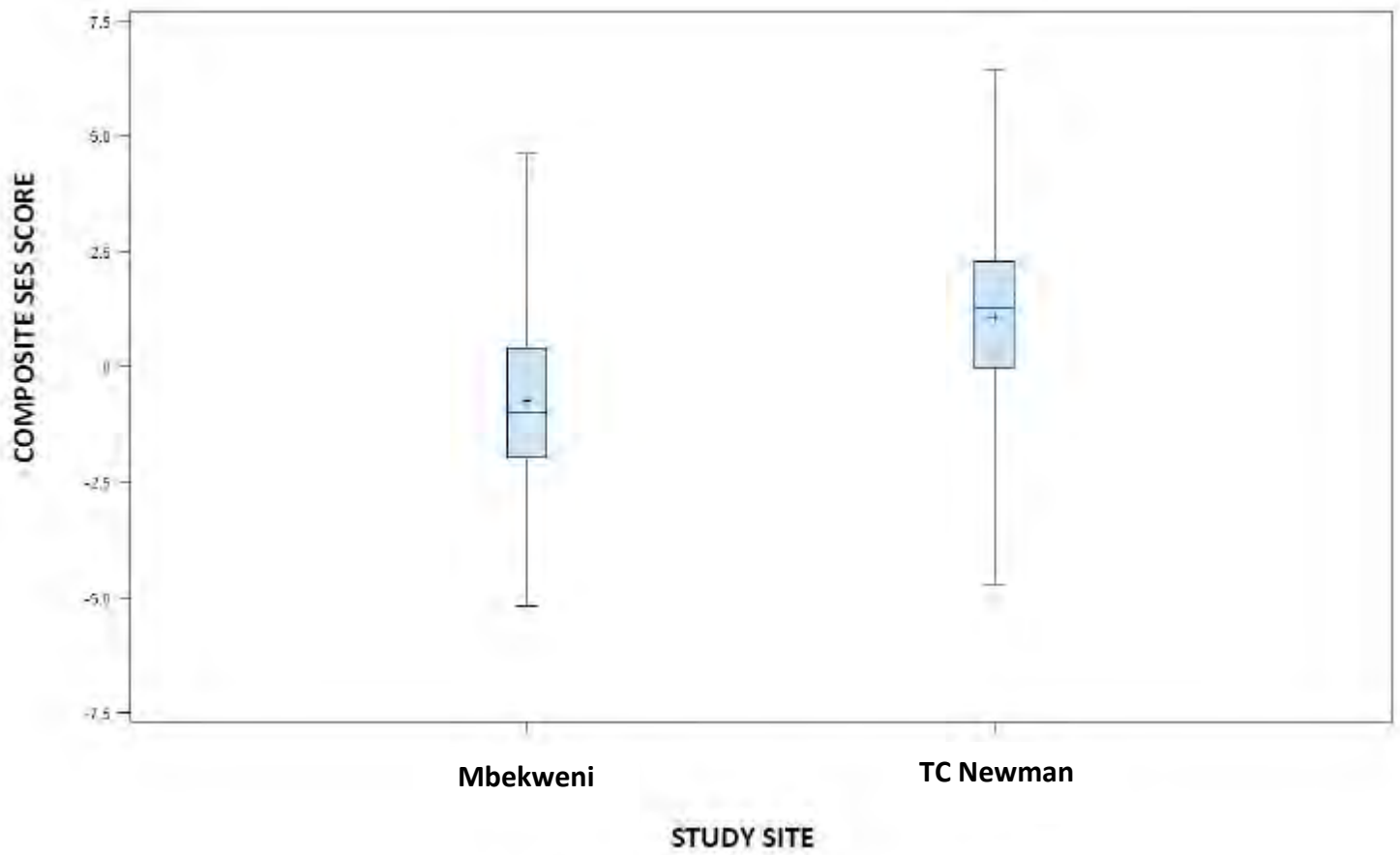
Women in this study sample ranged in age from 18 to 41 years, with a mean of 26 years. Sixty percent of the women were unmarried. Although participants were recruited without regard for ethnic or racial characteristics, approximately half of our study population self-reported as Mixed-Race (“Coloured”) and Afrikaans-speaking, with the remainder reporting as Black and isiXhosa-speaking. Most of the women (62%) were born in the Drakenstein sub-district, with the majority (84%) having received at least some high school education (Grades 8 – 12). Approximately a third of the sample was unemployed. Almost half (41%) of the women received social (governmental) assistance, with all of these participants specifying that this was in the form of a childcare grant. At the time of this analysis, almost two thirds (64%) of the women lived in a house or flat, with the majority (58%) residing in an urban setting. Once the composite continuous SES scores were calculated, participants were stratified into quartiles, ie. lowest, low-moderate, moderate-high, highest SES. While a slight preponderance (27%) was seen in the lowest stratum, participants were distributed fairly evenly across the four categories. However, the majority of participants at Mbekweni (73%) scored within the lowest and low-moderate quartiles, compared to the minority at TC Newman (30%). **Table 4.1** depicts sociodemographic characteristics for the total study sample; as well as site-specific features. **Figure 4.2** represents a comparison of the composite SES scores at each study site.

Table 4.1 Maternal sociodemographic characteristics

Variable	Mbekweni n (%)	TC Newman n (%)	Total n (%)^a
Mean age (years)	27.02 (6.20)	26.08 (5.58)	26.48 (5.86)
Ethnicity (self-reported)			
Black/African	118 (99.16)	3 (2.08)	121 (46.01)
Mixed-Race	1 (0.84)	141 (97.92)	142 (53.99)
Home language			
isiXhosa	115 (96.64)	2 (1.39)	117 (44.49)
Afrikaans	2 (1.68)	138 (95.83)	140 (53.23)
English	0	4 (2.78)	4 (1.52)
Shona	2 (1.68)	0	2 (0.76)
Marital status			
Single	71 (59.66)	85 (59.03)	156 (59.32)
Married/in a marriage-like relationship (eg. co-habiting; in a committed, long-term relationship)	48 (40.34)	59 (40.97)	107 (40.68)
Place of birth			
In Paarl	39 (32.77)	125 (86.81)	164 (62.36)
Outside of Paarl, in the Western Cape	9 (7.56)	14 (9.72)	23 (8.75)
Outside of the Western Cape, in South Africa	69 (57.98)	5 (3.47)	74 (28.14)
Outside of South Africa	2 (1.68)	0	2 (0.76)
Highest level of education			
Grades 1–7	15 (12.61)	11 (7.64)	26 (9.89)
Grades 8–12	98 (82.35)	122 (84.72)	220 (83.65)
Post-high school education	6 (5.04)	11 (7.64)	17 (6.46)
Employment status			
Unemployed	12 (10.08)	81 (56.64)	93 (35.50)
Homemaker/student	79 (66.39)	11 (7.69)	90 (34.35)
Employed	28 (23.53)	51 (35.66)	79 (30.15)
Financial assistance (governmental grant)			
No	68 (57.14)	85 (59.86)	153 (58.62)
Yes	51 (42.86)	57 (40.14)	108 (41.38)
Type of dwelling (current)			
Shack	66 (55.46)	6 (4.23)	72 (27.59)
Wendy house or backyard dwelling	1 (0.84)	22 (15.49)	23 (8.81)
House or flat	52 (43.70)	114 (80.28)	166 (63.60)
Living area (current)			
Urban	20 (17.09)	131 (92.25)	151 (58.30)
Rural	17 (14.53)	8 (5.63)	25 (9.65)
Township	80 (68.38)	3 (2.11)	83 (32.05)
Composite SES quartiles			
Lowest	53 (44.54)	20 (13.61)	73 (27.44)
Low-moderate	34 (28.57)	24 (16.33)	58 (21.80)
Moderate-high	18 (15.13)	50 (34.01)	68 (25.56)
Highest	14 (11.76)	53 (36.05)	67 (25.19)

^a Due to rounding, totals may not add to 100%.

Figure 4.2 Box-and-whisker comparison of composite SES scores at each study site



4.3.2 Biomedical, reproductive and psychosocial risk

For the vast majority of biomedical risk factors, prevalence rates were within the range of 0.5% to 2.5%, **Table 4.2**. Similarly, most participants scored low on each of the continuous measures of cumulative biomedical and reproductive risk. However, 20% of women were HIV positive at the time of data collection (based on the results of voluntary counseling and testing). Further, most women (81%) reported that the index pregnancy was unplanned, and almost two thirds (62%) were found to have experienced insufficient weight gain during pregnancy (defined as less than 0.3kg per week during the second and third trimesters) (Strauss & Dietz 1999).

The prevalence of psychopathological symptoms was also relatively high in this sample, with almost a third of participants scoring above threshold on the BDI-II and EPDS (measures of depression); while exactly a third screened positive for PTSD. While the continuous measure for alcohol consumption was relatively low in this study sample, tobacco use during pregnancy was common. The prevalence of substance use of participants at TC Newman was notably higher than at Mbekweni. In particular, tobacco use at TC Newman was far more prevalent (mean ASSIST score of 11.85 at TC Newman, compared to 2.15 at Mbekweni).

Table 4.2 Biomedical, reproductive and psychosocial risk factors

Variable	Number (%)	Mean (SD)
Biomedical risk factors		
HIV	53 (20.15)	
Asthma	6 (2.42)	
Urinary Tract Infection	6 (2.42)	
Tuberculosis	2 (0.81)	
Hypertension	2 (0.81)	
Hyperemesis gravidarum	2 (0.81)	
Diabetes mellitus	1 (0.40)	
Pelvic inflammatory disease	1 (0.40)	
Cardiovascular disease	0	
Cumulative medical risk		
0	111 (43.36)	
1	123 (48.05)	
2	20 (7.81)	
3	2 (0.78)	
Mean (SD)		0.66 (0.66)
Reproductive risk factors		
Poor maternal weight gain during current pregnancy	116 (62.03)	
Female sex of newborn	127 (48.66)	
Nulliparity	101 (38.11)	
Prior caesarean section	48 (18.05)	
Prior LBW infant	23 (8.68)	
Prior premature birth	15 (5.66)	
Prior intra-uterine death	3 (1.13)	
Current multiple gestation	0	
Cumulative reproductive risk		
0	54 (20.30)	
1	118 (44.36)	
2	84 (31.58)	
3	9 (3.38)	
4	1 (0.38)	
Mean (SD)		1.19 (0.81)
Psychosocial risk factors		
Unplanned pregnancy	214 (81.06)	
Depression & psychological distress		
BDI-II (dichotomous – above threshold)	66 (27.85)	
BDI-II (continuous)		13.95 (10.10)
EPDS (dichotomous – above threshold)	72 (30.38)	
EPDS (continuous)		9.76 (5.63)
SRQ-20 (dichotomous – above threshold)	52 (22.22)	
SRQ-20 (continuous)		4.88 (3.96)
Posttraumatic stress disorder		
MPSS (dichotomous – above threshold)	77 (33.33)	
Substance use (continuous measures)		
Alcohol		2.99 (7.44)
Tobacco		7.82 (11.30)

4.3.3 Exposure to trauma (see Table 4.3)

Almost half of the sample (48%) scored above threshold on the CTQ, with a mean continuous score of 41 (SD 14.5). This suggests a history of some form of abuse in childhood, with a low-to-moderate severity index. When considering the specific sub-categories assessed on this questionnaire, it was found that the domains of sexual abuse, emotional neglect and physical neglect were scored above threshold (low-moderate severity), when compared to data in the CTQ norm group (2,200 males and females from seven heterogeneous clinical and community samples, representing diverse sociodemographic strata) (Bernstein & Fink 1998).

Using dichotomised scoring, nearly a third of women (32%) reported a history of emotional IPV; and more than a quarter (28%) had experienced physical abuse during the previous 12 months. Past-year sexual abuse was reported in 14% of cases. Similarly, when lifetime IPV experiences were assessed on the four-point frequency scoring scale, almost half of the study sample (41%) reported emotional abuse; 37% reported physical abuse; and 12% reported sexual abuse.

4.3.4 Newborn outcomes (see Table 4.4)

The median (IQR) for birthweight was 3.07 (0.50) kg and for low WAZ score was -0.52 (IQR = 1.11). In addition, a notable clinic-specific difference was found in infant birthweight. The median (IQR) for mothers enrolled at TC Newman [3.02 (0.52) kg] was found to be lower than that of Mbekweni's infants [3.13 (0.47) kg]. When dichotomising birthweights at each clinic, it was found that the prevalence of LBW at TC Newman (17%) was significantly higher than that at Mbekweni (8%, $p = 0.022$). However, differences in dichotomised WAZ scores between sites again failed to show statistical significance.

Table 4.3 Childhood, lifetime and past-year trauma exposure

Variable	Number (%)	Mean (SD)	Interpretation
Childhood trauma			
CTQ dichotomous – above threshold	113 (47.88)		
CTQ continuous		40.59 (14.49)	
CTQ_emotional abuse (continuous)		8.33 (3.98)	None-minimal
CTQ_physical abuse (continuous)		7.14 (3.66)	None-minimal
CTQ_sexual abuse (continuous)		6.48 (3.59)	Low-moderate
CTQ_emotional neglect (continuous)		10.53 (5.04)	Low-moderate
CTQ_physical neglect (continuous)		8.10 (3.42)	Low-moderate
IPV (adult)			
Past-year IPV (dichotomous)			
Emotional IPV	73 (31.60)		
Physical IPV	66 (28.21)		
Sexual IPV	32 (13.68)		
Lifetime IPV			
Emotional IPV			
None	138 (58.72)		
Any Emotional IPV	97 (41.28)		
Low Frequency	21 (8.94)		
Mid Frequency	54 (22.98)		
High Frequency	22 (9.36)		
Physical IPV			
None	149 (63.40)		
Any Physical IPV	86 (36.59)		
Low Frequency	26 (11.06)		
Mid Frequency	44 (18.72)		
High Frequency	16 (6.81)		
Sexual IPV			
None	207 (88.09)		
Any Sexual IPV	28 (11.92)		
Low Frequency	5 (2.13)		
Mid Frequency	14 (5.96)		
High Frequency	9 (3.83)		

Table 4.4 Newborn outcomes

Variable		Mbekweni – n (%)	TC Newman – n (%)	Total – n (%)
Birthweight in kilograms (continuous)	Median (IQR)	3.13 (0.47)	3.02 (0.52)	3.07 (0.50)
Low birthweight (dichotomous)*	Number (%)	9 (7.56)	25 (17.01)	34 (12.78)
WAZ score (continuous)	Median (IQR)	-0.35 (1.02)	-0.66 (1.71)	-0.52 (1.11)
Low WAZ score (dichotomous)	Number (%)	8 (7.02)	21 (14.29)	29 (11.11)

* $p < 0.05$

4.3.5 Associations between exposure to trauma during pregnancy and newborn outcomes

Bivariate analyses were performed to determine the correlations between a number of trauma-related risk factors and subsequent newborn outcomes. Predictor variables were those pertaining to maternal sociodemographics (age, marital status, income); biomedical risk (height, and composite medical and reproductive risk); psychosocial risk (pregnancy intention, contraceptive use, degree of partner support, depression, PTSD and substance use); and trauma exposure (childhood trauma, lifetime IPV and past-year IPV). Outcome variables were LBW and low WAZ scores (expressed as continuous and dichotomous variables). A number of statistically significant correlations were found, **Table 4.5**.

Women with a history of past-year physical IPV exposure were more likely to deliver infants with LBW ($r = 0.21$; $p = 0.001$) and with low WAZ scores ($r = 0.18$; $p = 0.006$). Further, a history of lifetime physical IPV exposure was found to be associated with both low infant birthweight ($r = 0.13$; $p = 0.047$) and low WAZ scores ($r = 0.14$; $p = 0.041$). Neither sexual nor emotional IPV exposure (past-year or lifetime) yielded significant associations with the outcomes of interest.

Maternal anthropometry and substance use also emerged as important risk factors for low infant birthweight. Maternal height was found to be significantly associated both with birthweight ($r = 0.16$; $p = 0.009$) and with WAZ scores ($r = 0.17$; $p = 0.007$); as was alcohol use (association with birthweight: $r = -0.19$; $p = 0.003$; association with WAZ score: $r = -0.18$; $p = 0.006$). Maternal tobacco use was found to be significantly associated with all four major outcomes of interest – with birthweight ($r = -0.22$; $p = 0.0006$); WAZ score ($r = -0.23$; $p = 0.0004$); LBW ($r = 0.2$; $p = 0.002$); and low WAZ score ($r = 0.15$; $p = 0.02$). However, neither depression nor PTSD showed significant correlations with these outcomes.

In the final regression analyses, outcomes of interest were LBW and low WAZ scores; while the predictor variable was past-year physical IPV exposure. (As neither emotional nor sexual abuse showed significant correlations with these outcomes of interest on bivariate analyses, these subtypes were not included as predictor variables in the final regression models.) Both models

were controlled for study site (clinic), maternal height, ethnicity, SES, tobacco use, alcohol use and childhood trauma, due to the effects of these variables on the outcomes of interest. The final regression model run was significant [$r^2 = 0.14$ (adjusted $r^2 = 0.11$, $F(8,212) = 4.16$, $p = 0.0001$]. Exposure to physical IPV occurring during the past year was found to be significantly associated with LBW [$t = -2.04$, $p = 0.0429$], when controlling for these potential confounders, **Table 4.6**. A significant association with decreased WAZ scores was not demonstrated.

Table 4.5 Bivariate analyses of the correlation between a number of trauma-related risk factors and newborn outcomes

Pearson correlation coefficients

Prob > |r| under H0: Rho = 0

Number of Observations

	Sociodemographics			Biomedical Risk			Psychosocial Risk				
	Age	Marital status	Income	Height	Composite medical risk	Composite reproductive risk	Pregnancy intention	Contraceptive use	Partner support	Tobacco	Alcohol
Birthweight	0.03250	-0.03831	-0.01912	0.16006	-0.05180	0.01513	-0.03944	0.01094	-0.06240	-0.22291	-0.19257
	0.6179	0.5362	0.7599	0.0093*	0.4092	0.8059	0.5234	0.8596	0.3515	0.0006*	0.0032*
	238	263	258	263	256	266	264	264	225	233	233
WAZ	0.03641	-0.03410	-0.02365	0.16884	-0.06443	0.07686	-0.04786	0.00367	-0.06617	-0.23418	-0.18142
	0.5795	0.5857	0.7081	0.0066*	0.3093	0.2158	0.4431	0.9532	0.3275	0.0004*	0.0060*
	234	258	253	258	251	261	259	259	221	228	228
LBW	-0.04602	0.06015	0.01174	-0.10513	-0.02683	-0.00724	0.04504	0.04969	0.07443	0.19976	0.10378
	0.4798	0.3312	0.8512	0.0888	0.6692	0.9065	0.4662	0.4214	0.2662	0.0022*	0.1141
	238	263	258	263	256	266	264	264	225	233	233
Low WAZ	-0.05286	0.01257	-0.00436	-0.11495	-0.02380	-0.02510	0.04732	0.06787	0.09203	0.15135	0.10210
	0.4209	0.8408	0.9450	0.0653	0.7075	0.6865	0.4483	0.2765	0.1728	0.0223*	0.1242
	234	258	253	258	251	261	259	259	221	228	228

Pearson correlation coefficients

Prob > |r| under H0: Rho = 0

Number of Observations

	Depression			Trauma Exposure & PTSD							
	BDI-II	EPDS	SRQ-20	Childhood trauma	Emotional IPV (lifetime)	Physical IPV (lifetime)	Sexual IPV (lifetime)	Emotional IPV (past-year)	Physical IPV (past-year)	Sexual IPV (past-year)	PTSD
Birthweight	-0.06380 0.3281 237	-0.00570 0.9305 237	-0.04561 0.4875 234	-0.00910 0.8894 236	-0.09418 0.1501 235	-0.15920 0.0146* 235	-0.08001 0.2217 235	-0.07844 0.2350 231	-0.14761 0.0239* 234	-0.08612 0.1893 234	-0.00364 0.9562 231
WAZ	-0.04060 0.5383 232	-0.00408 0.9507 232	-0.02266 0.7331 229	-0.01135 0.8637 231	-0.10113 0.1262 230	-0.15502 0.0187* 230	-0.08901 0.1786 230	-0.06568 0.3256 226	-0.13623 0.0394* 229	-0.09746 0.1415 229	0.01736 0.7948 227
LBW	-0.08664 0.1837 237	0.02454 0.7070 237	-0.03689 0.5745 234	-0.02140 0.7437 236	0.03849 0.5572 235	0.12961 0.0472* 235	0.10801 0.0986 235	0.11147 0.0910 231	0.20782 0.0014* 234	0.08320 0.2048 234	-0.02858 0.6656 231
Low WAZ	-0.07450 0.2584 232	0.05233 0.4276 232	0.00013 0.9984 229	0.04125 0.5328 231	0.07359 0.2664 230	0.13511 0.0406* 230	0.09751 0.1404 230	0.10285 0.1232 226	0.18039 0.0062* 229	0.07484 0.2594 229	-0.04017 0.5471 227

* $p < 0.05$

Table 4.6 Multiple linear regression analyses of the association between exposure to IPV during the past year and newborn outcomes

	Model 1: Multiple linear regression of the association between past-year IPV exposure and LBW	Model 2: Multiple linear regression of the association between past-year IPV exposure and low WAZ score
	B (SE)	B (SE)
Recent IPV exposure	-0.15 (0.07)*	-0.30 (0.17)
Study site (Mbekweni)	-0.49 (0.28)	-0.79 (0.63)
Ethnicity (Black/African)	0.56 (0.28)*	1.01 (0.63)
Height	0.01 (0.004)*	0.03 (0.01)*
SES	0.02 (0.02)	0.05 (0.04)
Tobacco	-0.006 (0.003)	-0.01 (0.008)
Alcohol	-0.008 (0.004)	-0.02 (0.01)
Childhood Trauma	0.001 (0.002)	0.002 (0.005)

* $p < 0.05$

4.4 Discussion and conclusions

The main findings of our study were 1) a large proportion of our study sample was found to have experienced past-year IPV, with exposure to emotional IPV most frequently reported, followed by physical, and then sexual abuse; 2) a notable clinic-specific difference was found in infant birthweight. The median (IQR) for mothers enrolled at TC Newman was found to be lower than that of Mbekweni's infants. When dichotomising birthweights at each clinic, it was found that the prevalence of LBW at TC Newman was significantly higher than that at Mbekweni. However, differences in dichotomised WAZ scores between sites failed to show statistical significance; 3) in this study sample, LBW was found to be significantly predicted by past-year maternal IPV exposure, when controlling for study site (clinic), maternal height, ethnicity, SES, substance use and childhood trauma. A significant association with decreased WAZ scores was not demonstrated.

The high prevalence of IPV in our sample is largely consistent with other studies conducted in LMIC regions. For example, in their recent critical review of studies conducted outside of Canada and the United States, Campbell and colleagues (2004) reported comparatively higher rates of IPV during pregnancy in LMIC regions (31.5% in Egypt, 21% to 28% in India, and 21% in Saudi Arabia), when compared to HIC countries (prevalence rates ranging from 3.4% to 11.0%). Data from the large WHO Multi-Country Study on Women's Health and Domestic Violence against Women (García-Moreno et al. 2005, 2006) have supported these findings. This study enrolled 24,000 women from 15 sites in 10 culturally diverse countries — Bangladesh, Brazil, Ethiopia, Japan, Namibia, Peru, Samoa, Serbia and Montenegro, Thailand, and the United Republic of Tanzania. The consistency of methodology used in all countries allowed a valid cross-cultural comparison and provided valuable insight into regions from which few data were available previously. A wide variation in IPV prevalence between settings was noted in this study, with comparatively lower rates reported in HIC regions such as Japan (with a 13% lifetime prevalence of physical IPV and 6% of sexual IPV) versus LMIC areas such as Peru (61% of the study population reported physical IPV) and Ethiopia (59% reported sexual IPV). Further, in countries where both large industrialised (urban) and rural regions were studied, IPV levels

were found consistently to be higher in the rural populations. It seems thus that women in LMIC regions (such as South Africa) are at greater risk of IPV exposure during pregnancy than are those in HIC countries.

The varying prevalence of IPV subtypes in our study population is also noteworthy. In a prospective cohort study of 838 women post-delivery in a Chinese university teaching hospital (Leung et al. 2002), it was found that 16.6% of women (n = 139) had experienced recent abuse, with 87 of these (10.4%) having been abused in the index pregnancy. While these prevalence rates are somewhat lower than in our study sample, most reported cases were of verbal/emotional abuse, a finding echoed in our population. This is noteworthy, as most literature to date has focused on physical and/or sexual IPV, with a relative paucity of data on the impact of verbal/emotional abuse on health outcomes.

Of the three domains of abuse, Leung and colleagues (2002) also reported the prevalence of sexual abuse (1.7%, n = 14) to be the lowest. While this is again lower than was found in our study (14% of our participants had experienced past-year sexual abuse), it is noteworthy that sexual abuse appears to be less prevalent than either physical or emotional/verbal abuse in both study samples. One explanation may be under-reporting by study participants, based either on the narrow definition of sexual abuse in the IPV questionnaire (ie. forced sexual acts) (see Silverman et al. 2007) or on the widespread stigma associated with this subtype of abuse.

To the best of our knowledge, ours is the first study to examine the prevalence of IPV during pregnancy and its association with low infant birthweight in the South African setting. In our study sample, the median newborn birthweight was found to be within the normal WHO parameters (WHO 1995, 2013b). This is in contrast to the recent WHO/UNICEF (United Nations Children's Fund) report on country, regional and global estimates of LBW prevalence rates (UNICEF & WHO 2004), which cited the global LBW rate (LBWR) as approximately 15.5%. In Africa, the reported prevalence is 14.3%; and 15.4% in South Africa (UNICEF & WHO 2004; MRC et al. 2003). However, in a recent MRC (Medical Research Council) Saving Babies Report (2003), a LBWR of 19.8% was cited for the Western Cape. The more significant discrepancy between our findings and this provincial estimate may be attributed to a number of factors. First, the

MRC data may be skewed by the much higher LBWR in rural areas in the province. Second, the majority of our study population has received at least some high school education (Grades 8 – 12). This is relatively high when compared to data published elsewhere. For example, in the South African Demographic and Health Survey (SADHS), a cross-sectional nationally representative study of 13,089 adult men and women (Puoane et al. 2002), it was found that only 11.8% (n = 913) of female participants had completed Grade 12 (secondary education). Third, due to the longitudinal cohort design of the larger DCHS, enrolled women enter into the healthcare system early in their antenatal course, and are followed up throughout pregnancy, delivery and the postpartum period. Thus, participants have improved access to antenatal care and health education which otherwise may not have been available to them.

In our study, site-specific differences in infant birthweights were also found, with those at TC Newman lower than those at Mbekweni. A number of interrelated factors may explain these differences. For example, the prevalence of substance use among pregnant women was notably higher at TC Newman than at Mbekweni. In particular, tobacco use at TC Newman was far more prevalent. Further, in the final regression models, tobacco use was found to be significantly associated with LBW and with low WAZ scores. The association between smoking during pregnancy and adverse infant outcomes has been well-documented in both HIC and LMIC settings. For example, in their early cohort study of 5,166 mother-infant dyads in Pelotas, Brazil, Horta and colleagues (1997) reported that infants whose mothers had smoked during pregnancy were significantly more likely to have LBW than those of non-smoking mothers (OR 1.59; 95% CI: 1.30; 1.95). Further, it was found that the average birthweight of these infants was 142g lower than that of the non-smoking-exposed group. While no association between smoking and preterm delivery was reported, smoking was found to be significantly associated with IUGR (OR 2.07; 95% CI: 1.69; 2.53). More recently, similar findings were reported by Jaddoe and colleagues (2008). In their nested sub-study of the Generation R Study, a population-based prospective cohort investigation of 7,098 mother-infant pairs conducted in the Netherlands, these authors found that active smoking during pregnancy was significantly associated with both LBW (adjusted OR 1.75; 95% CI: 1.20; 2.56) and preterm birth (adjusted

OR 1.36; 95% CI :1.04, 1.78). It was also found that active maternal smoking late in pregnancy was associated most strongly with these adverse outcomes.

A significant site-specific difference in composite SES scores was also noted. As this variable is a comprehensive indicator of education, employment status, household income and access to resources and assets, it suggests a notable contextual difference between study sites. There is some evidence that low SES may contribute to increased risk both of IPV (Cunradi et al. 2002) and of low infant birthweight (Parker et al. 1994). In their recent systematic review of 106 studies conducted in industrialised countries, Blumenshine and colleagues (2010) reported a significant association between low socioeconomic measures and adverse birth outcomes such as LBW and preterm delivery. Socioeconomic disadvantage and disparities were found to be associated consistently with increased risk across socioeconomic measures, birth outcomes and countries. In our study population, however, the site with higher SES had the higher prevalence of low birthweight infants. This presumably reflects the fact, noted above, that tobacco use is higher in the higher SES site.

In our study, maternal IPV (physical) exposure was found to be significantly associated with low infant birthweight. While there has been a paucity of data examining the association between IPV and adverse infant outcomes in LMIC regions such as South Africa, the data here are consistent with three large studies conducted in Brazil (Ferri et al. 2007), Mexico (Valdez-Santiago & Sanín-Aguirre 1996) and Uganda (Kaye et al. 2006). In the latter study, Kaye and colleagues (2006) conducted a prospective cohort investigation of 612 women enrolled in the second trimester of pregnancy and followed up until birth. Of these women, 27.7% (n = 169) reported IPV exposure during pregnancy, and delivered infants with a mean birthweight 186g lower than that of their non-exposed counterparts. Further, these authors reported that the relative risk of a LBW delivery among IPV-exposed women was 3.78 (95% CI: 2.86; 5.00). Additional obstetric complications in this subgroup included hypertension and premature rupture of membranes. While no significant association between IPV exposure and low newborn WAZ scores was demonstrated, it should be noted that LBW and WAZ scores are discrete constructs, and thus may be expected to differ slightly. Nonetheless, both outcomes

reflect the adverse effect of IPV exposure during pregnancy. Thus, further work on underlying mechanisms would be useful to delineate whether the slight differences noted here are due to chance, or in fact reflect meaningful pathophysiological differences.

How, then, does trauma exposure in women (either during pregnancy or across the lifespan), increase the risk of delivering a LBW infant? To date, this association has been attributed to a number of direct and indirect mechanisms. First, abdominal trauma and consequent placental damage and premature uterine contractions or rupture of membranes may explain a direct causal association (Newberger et al. 1992; Campbell et al. 1999). Further, infection or genital trauma resulting from forced sexual activity may increase the risk of adverse infant outcomes. There is also a growing body of evidence for the role of the HPA-axis in mediating LBW delivery in abused women. It has been suggested that pregnant women exposed to psychosocial trauma experience HPA-axis hyperactivity, thus resulting in increased circulating cortisol. This stress hormone then has a transplacental inhibitory effect on intra-uterine foetal growth (Campbell et al. 1999; Sandman et al. 1997). Further, increased levels of CRH (corticotropin-releasing hormone, which is secreted by the hypothalamus in response to stressful stimuli) may also be associated with premature delivery (Sandman et al. 1997).

Indirect environmental mechanisms may include lack of intimate partner support, substance abuse, maternal mental illness and low SES (Campbell et al. 1992; Murphy et al. 2001). While the degree of partner support did not show a significant correlation with low infant birthweight in our study sample, maternal substance use was found to be an important potential confounder in the association between IPV and LBW. Thus, both tobacco and alcohol use were controlled for in the final regression analyses. As already discussed, there is a strong body of work documenting the detrimental effect of smoking on pregnancy and newborn outcomes. Further, perinatal alcohol consumption has been shown to increase the risk of delivering a LBW infant. For example, in their recent systematic review and meta-analysis, Patra and colleagues (2011) reported a dose–response relationship — heavy alcohol consumption during pregnancy was found to increase the risk of LBW, preterm delivery and a SGA infant, while light to moderate alcohol consumption showed no effect.

Additional mediators of the association between IPV and LBW may include low SES and maternal mental illness. Both factors are relevant to our economically disadvantaged study sample, in which depressive and posttraumatic symptoms are particularly prevalent. However, neither maternal depression nor PTSD showed a statistically significant correlation with our outcomes of interest in bivariate analyses. The current body of work assessing the association between maternal psychopathology and LBW also remains somewhat inconsistent, possibly due to diverse definitions and measurements of maternal mental illness; as well as little attention paid to potential confounders (Alder et al. 2007). For example, while our study group previously demonstrated strong associations between maternal antenatal depression and reduced infant WAZ scores and HCAZ scores at birth in the unique Drakenstein cohort (Brittain et al. 2015 – see also *Chapter 3, Section 3.4 – Discussion and conclusions, p 40*); a recent systematic review and meta-analysis of thirty studies (Grigoriadis et al. 2013) revealed a significant – but modest – association with increased odds of premature delivery and decreased breastfeeding initiation; but no associations with birth weight or LBW in the main analyses.

This study is limited by a number of methodological and analytical factors. First, it is a cross-sectional analysis, and causality is difficult to determine. Second, much of the data concerning antenatal risk factors are dependent on participant self-report. Thus, reporting bias may have led to inaccuracies in prevalence rates of trauma exposure and related variables. Third, data were collected from just one sub-district in South Africa, thus limiting national (and international) generalisability. Fourth, our insights may be limited by the relatively small sample size, high levels of attrition and subsequent reduced statistical power to detect small associations. Data from a notable number of participants ($n = 56$) were omitted from analyses due to poor quality. Given the small sample size, false negative findings cannot be excluded. However, the study was powered adequately to detect clinically meaningful effect sizes, and in turn, several significant associations emerged in the analysis. Thus, our study provides a valuable complement to the small but growing body of work on the association between IPV during pregnancy and LBW in LMIC regions. Fourth, unmeasured confounders may have contributed to our study findings, although we attempted to minimise residual confounding by adjusting for key variables such as study site and SES. Finally, we do not measure non-IPV

trauma exposure during pregnancy. While this was a purposeful attempt at a more precise and focused investigation of the *sequelae* of IPV, an assessment of all types of violence or trauma to which women may be exposed would be a helpful inclusion in future studies. This potentially could delineate whether exposure to any violence/trauma (as opposed to IPV specifically) during pregnancy significantly predicts delivery of a LBW infant.

Future structured longitudinal studies would also be of value in addressing the causal mechanisms between maternal exposure to abuse, and subsequent adverse infant outcomes. Further, an assessment of maternal health outcomes would be a useful addition to this body of work. Methodological adjustments to assessment tools may also be warranted. For example, standardised and cross-culturally valid definitions of IPV could improve data quality (Ballard et al. 1998; Murphy et al. 2001). Finally, a more comprehensive investigation of the role of protective environmental factors (eg. intimate partner support) should be addressed in future studies, in order to enhance our findings and the current evidence base (Ferri et al. 2007).

Such additions to the research field would help to clarify the association between antenatal IPV exposure and low infant birthweight, thus informing not only scientific knowledge but also clinical decision-making and public health policies. Many of the recommendations outlined in the WHO Multi-Country Study (García-Moreno et al. 2005, 2006) hold promise. In all cases, intersectoral and multidisciplinary collaborations seem key in translating empirical data into tangible interventions. For example, a comprehensive primary prevention programme would be integral to minimising the downstream *sequelae* of IPV. Strategies may include multimedia messages to increase public awareness, alter entrenched gender-related prejudices, reduce IPV-related stigma and enhance informal community support networks. The target audience of such campaigns should include both women and men, and efforts could be carried out in schools, healthcare facilities and workplaces. Primary prevention may also take the form of liaison with the police services and local government to ensure a safer physical environment for women. “High-risk” locales should be identified and resources dedicated to enhance the safety of such areas, eg. by improved lighting and/or increased police presence.

Secondary preventative strategies are also important to support and assist women exposed to IPV. As discussed by García-Moreno and colleagues (2005, 2006), the public health sector should be mobilised to respond to and manage the multidimensional effects of such abuse. Training of healthcare workers at all service levels should occur to ensure appropriate first-line support of women reporting IPV, as well as appropriate referral when necessary. Again, close collaboration with non-healthcare sectors (eg. the police and/or legal services) will be essential in developing a comprehensive care network. Of particular relevance to our study are reproductive health services which should be sensitised to contribute to this network. Antenatal booking presents a unique entry point for pregnant women to access care, and for healthcare workers to provide a safe, confidential and supportive environment for women exposed to IPV during pregnancy.

More broadly, informal and formal support networks for victims of IPV should be strengthened. Unfortunately, resource constraints (particularly in rural areas) continue to limit the availability and accessibility of this crucial level of care. In addition to governmental commitment to improving formal services (eg. social workers, psychologists, counsellors and shelters), informal sources of support such as community leaders should be mobilised. Women may well be more willing to disclose abuse in a less formal milieu, and the involvement of community members would be useful in decreasing the social stigma and shame associated with IPV.

Finally, ongoing support for IPV-related research is essential to inform these and other public health interventions. Data on the causes, prevalence and *sequelae* of IPV during pregnancy are needed to provide a compelling basis for action. In particular, culturally-specific modifiable risk factors for abuse that are amenable to intervention should be identified and targeted. In LMIC and resource-constrained regions, support from non-governmental and private donors may well be necessary to supplement governmental commitment. Ultimately, studies such as ours aim to provide a deeper understanding of the magnitude, aetiology and impact of IPV during pregnancy, and to contribute to improved primary and secondary prevention strategies.

In the next chapter – based on *Publication 3* – the association between maternal psychological trauma such as IPV exposure (and other psychiatric symptoms and stressors), and poor infant neurodevelopment at age 6 months, will be discussed. This discussion will address the third research objective of this thesis.

CHAPTER 5

PUBLICATION 3

Intimate partner violence and other psychiatric symptoms and stressors as predictors of poor developmental outcomes in infancy in the Drakenstein Child Health Study

Authors

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Synopsis

This chapter addresses directly Research Objective 3 of this thesis (*see Chapter 1, Section 1.6 – Study objectives and related publications, p 6*):

To determine the association between maternal trauma exposure and poor infant neurodevelopment at age 6 months in the study cohort.

While a significant association between maternal alcohol consumption during pregnancy and poor infant developmental outcomes was noted, the key finding of this publication in relation to this thesis was that maternal exposure to past-year sexual IPV may be associated with poor infant neurodevelopment. Thus, this is in keeping with the research objective, above. The manuscript on which this chapter is based was submitted to a special issue of the *Journal of Health Psychology (JHP)*, focusing on Health Psychology in Africa and is currently under review.

Abstract

Introduction

Maternal psychiatric disorders and exposure to psychosocial stressors during pregnancy may be associated with poor development in early childhood. Despite the high burden of maternal stressors and of poor childhood development in LMIC settings, there remains a paucity of data from these regions. We investigated the association between antenatal exposure to psychosocial stressors, and infant development in the DCHS.

Methods

Antenatal symptoms and stressors were assessed using reliable, validated questionnaires. Predictor variables pertained to maternal sociodemographics; general medical health; psychiatric symptoms and stressors; and infant anthropometry and growth velocity. Infant developmental outcomes at age 6 months were assessed using the Bayley Scales of Infant and

Toddler Development. Bivariate and multiple regression analyses were used to determine the association between predictor and outcome variables.

Results

105 mother-infant dyads were studied. The regression model predicting fine motor development reached significance [$r^2 = 0.20$ (adjusted $r^2 = 0.13$, $F(8,88) = 2.75$, $p = 0.0094$), with maternal exposure to past-year sexual IPV [$t = -2.86$, $p = 0.005$] and alcohol use during pregnancy [$t = -2.29$, $p = 0.02$] each found to be significant for predicting poor outcome in infant fine motor development, when controlling for clinic site, marital status, SES, depression, PTSD and tobacco use.

Conclusion

Exposure to past-year sexual IPV and antenatal alcohol use each may affect infant development. However, given the methodological limitations in this exploratory study, there is a need for further research in this field to replicate these findings, to elucidate the underlying neurobiology and to develop effective preventative strategies.

Keywords: Intimate partner violence, alcohol, pregnancy, infant neurodevelopment, South Africa

5.1 Introduction

Maternal exposure to psychosocial stressors (such as IPV), as well as psychiatric disorders and symptoms (such as alcohol and substance use disorders) during pregnancy constitute an important public health concern; and may be associated with poor pregnancy outcomes and childhood developmental delay (Testa et al. 2003; Shamu et al. 2011; Shah et al. 2010). In two recent Lancet series (Grantham-McGregor et al. 2007; Walker et al. 2007, 2011; Engle et al. 2007, 2011; Lake 2011), it was estimated that more than 200 million children under age 5 years fail to reach their potential in cognitive development in developing countries.

As discussed in *Chapter 4 – Publication 2 (p 42-72)* (see also Koen et al. 2014), maternal exposure to IPV during pregnancy has emerged as an important predictor of adverse outcomes. For example, in their recent meta-analysis and systematic review of studies conducted in HIC settings, Murphy and colleagues (2001) found that women reporting physical, sexual or emotional abuse during pregnancy were 1.4 times more likely than non-abused women to give birth to a baby with LBW (95% CI: 1.1; 1.8).

The detrimental effects of substance use during pregnancy have also been investigated widely. In a recent systematic review and meta-analysis of the dose–response relationship between alcohol consumption before and during pregnancy, and birth outcomes, it was reported that heavy prenatal alcohol use increases the risk of LBW, preterm delivery and SGA (Patra et al. 2011). Prenatal alcohol consumption is also associated with adverse developmental and neuropsychological outcomes in infancy and early childhood (Mattson et al. 2011, 2013; Adnams et al. 2001). In their meta-analytical review, Testa and colleagues (2003) found that foetal alcohol exposure at three levels of daily exposure (ie. less than 1 drink; 1 – 1.99 drinks; and 2 or more drinks) was associated with a significantly lower mental development index among infants aged 12 to 13 months.

In addition to IPV exposure and substance use, a number of other factors may contribute to predicting poor developmental outcomes in the LMIC setting. These include lack of pregnancy intent, decreased social support, societal violence, malnutrition, inadequate cognitive

stimulation and maternal stress and psychopathology (Hobel et al. 2008; Dominguez et al. 2005; Goldenberg et al. 1997; Shah et al. 2011; Walker et al. 2007, 2011). In their recent review, Van den Bergh and colleagues (2005) reported a direct link between antenatal maternal stress and anxiety (as measured by questionnaires and biological indicators of HPA-axis dysfunction) and cognitive, behavioural and emotional problems in childhood. It is possible that exposure to multiple stressors, over a long period of time, exerts a compound effect.

Despite the high burden of stressors and symptoms during pregnancy, and of adverse infant and developmental outcomes in the LMIC setting, there remains a paucity of data from developing countries such as South Africa. The purpose of the current analysis was to address predictors of outcomes at age 6 months.

5.2 Methods

This study reported data from the DCCHS – see *Chapter 2 – General Methodology (p 9-21)*. The analysis is for the period March 2012 to August 2013. Details of participant enrollment can be found in *Chapter 2, Section 2.3 – Participant recruitment and follow-up (p 9-10)*; and ethical processes relevant to this study in *Chapter 2, Section 2.5 – Ethical considerations (p 20-21)*. This study was also approved by the institutional review board at the University of California, Los Angeles (UCLA).

5.2.1 Measures

Maternal assessment

All assessment tools have been described in detail in *Chapter 2, Section 2.4 – Measures and variable calculation (p 10-18)*. For the purposes of this analysis, maternal sociodemographic characteristics; medical and reproductive health; alcohol and substance use (using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)); and psychiatric symptoms and stressors (using the Intimate Partner Violence questionnaire, Childhood Trauma Questionnaire (CTQ), Beck Depression Inventory II (BDI-II), Edinburgh Postnatal Depression Rating Scale (EPDS), SRQ-20, and the Modified PTSD Symptom Scale (MPSS)) were assessed, as has been described elsewhere (Zar et al. 2015; Stein et al. 2015; Koen et al. 2014). Those participants identified with a high burden of psychiatric symptoms or stressors and/or with suspected substance use during pregnancy were referred to service providers in the health system.

Infant outcomes

Anthropometric variables (weight, height and HC) at infant age 6 months were measured by trained clinical staff at the study clinics and z-scores calculated (see also *Chapter 2, Section 2.4 – Measures and variable calculation (p 18)*). Growth velocity from birth to infant age 6 months (weight and HC) was represented by the difference between sex-specific z-scores at these two time points. Following the WHO conventions, those infants falling two or more standard deviations from the mean were classified as having severe growth failure (WHO 2014). For our

purposes, all outcomes of interest at each timepoint (ie. low WAZ scores, HC for age, low HCAZ scores, 0 – 6 month growth velocity, and severe growth failure) were expressed as dichotomous and continuous variables.

Markers of infant development were assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) (Bayley, 2006a) – *see Chapter 2, Section 2.4 - Measures and variable calculation (p 19-20)*. For our analyses, a clinically significant developmental effect on the Bayley II scales was represented both as dichotomous and continuous variables.

5.2.2 Statistical analyses

Frequency distributions were used to describe sociodemographic variables of interest (age, marital status, income); general medical health (composite biomedical and reproductive health); psychiatric symptoms and stressors (pregnancy intention, degree of partner support, depression and PTSD, and childhood and/or adult trauma exposure); alcohol and substance use; infant anthropometry; and adverse infant outcomes. Bivariate analyses (Pearson correlation coefficients) were then applied to determine correlations between relevant predictor variables and markers of poor developmental outcomes across any of the Bayley-III subtests. Predictor variables (and potential confounders) were selected based on modelling informed by acyclic graphs built prior to conducting these analyses. Thereafter, those variables yielding statistically significant bivariate correlations were included in a number of multiple regression models.

5.3 Results

5.3.1 Sample size

At the time of analyses, 830 women had been enrolled, while 428 infants had reached 6 months of age. Of these 428 mother-infant dyads, a random sub-sample was selected to undergo Bayley-III assessment at this timepoint. Thus, 125 infants had undergone the Bayley-III assessment at the time of analysis. Data from an additional 20 participants were omitted due to lack of quality control, most of which arose in the first few months of data collection. The final sample for this analysis comprised 105 mother-infant dyads.

5.3.2 Maternal sociodemographic characteristics

Women in this study sample had a mean age of 26 years, with almost 70% being unmarried, **Table 5.1**. Most (93%) had received some high school education (Grades 8 – 12), but almost half (43%) was unemployed. Participants were distributed fairly evenly across the four socioeconomic categories. Most participants at Mbekweni (62%) scored within the lowest and low-moderate quartiles, compared to the minority at TC Newman (44%).

5.3.3 Biomedical and reproductive health

For the majority of biomedical risk factors, prevalence rates were within the range of 2.9% to 5.7%, **Table 5.2**. Most participants scored low on the continuous measures of cumulative biomedical and reproductive risk. However, approximately 13% of women were HIV positive at the time of data collection; and most women (80%) reported that the index pregnancy was unplanned.

5.3.4 IPV exposure and other psychiatric symptoms and stressors

Using dichotomised scoring, approximately a third of women (35%) reported a history of past-year emotional IPV; and a quarter reported exposure to past-year physical abuse. Past-year sexual abuse was reported in 7% of cases, **Table 5.3**. A site-specific difference in the prevalence rate of past-year IPV was found. Women at TC Newman reported higher levels of exposure to

emotional abuse (38% versus 26% at Mbekweni); to physical abuse (27% versus 20%); and to sexual abuse (10% versus 0) during the past year. Almost 40% of the study sample scored above threshold on the CTQ, with a mean continuous score of 38 (SD 14.5). This suggests a history of some form of abuse in childhood, with a minimal to moderate severity index. More than a quarter of participants scored above threshold on the Beck Depression Inventory II (BDI-II) and Edinburgh Postnatal Depression Rating Scale (EPDS); while almost a quarter (22%) screened positive for PTSD, **Table 5.3**.

Almost half (44%) of participants reporting smoking cigarettes during pregnancy, and 12% reporting prenatal alcohol consumption, **Table 5.3**. A site-specific difference was also found – 61% of participants at TC Newman reported tobacco use, compared to only 3% at Mbekweni; while 15% at TC Newman consumed alcohol, versus 6% at Mbekweni. This difference was also reflected in the mean continuous ASSIST scores for each study site.

Table 5.1 Sociodemographic characteristics

Variable	Mbekweni n (%)	TC Newman n (%)	Total n (%)^a
Mean age (years)	28.07 (5.50)	25.46 (4.87)	26.23 (5.18)
Ethnicity (self-reported)			
Black/African	31 (100)	0 (0)	31 (29.52)
Mixed-Race	0 (0)	74 (100)	74 (70.48)
Home language			
isiXhosa	31 (100)	0 (0)	31 (29.52)
Afrikaans	0 (0)	73 (98.65)	73 (69.52)
English	0 (0)	1 (1.35)	1 (0.95)
Marital Status			
Single	24 (77.42)	48 (64.86)	72 (68.57)
Married/in a marriage-like relationship (eg. co-habiting; in a committed, long-term relationship)	7 (22.58)	26 (35.14)	33 (31.43)
Place of Birth			
In Paarl	14 (45.16)	66 (89.19)	80 (76.19)
Outside of Paarl, in the Western Cape	4 (12.90)	6 (8.11)	10 (9.52)
Outside of the Western Cape, in South Africa	13 (41.94)	2 (2.70)	15 (14.29)
Highest Level of Education			
Grades 1-7	2 (6.45)	2 (2.70)	4 (3.81)
Grades 8-12	27 (87.10)	71 (95.95)	98 (93.33)
Post-high school education	2 (6.45)	1 (1.35)	3 (2.86)
Employment Status			
Unemployed	0 (0)	44 (60.27)	44 (43.14)
Homemaker/student	25 (86.21)	8 (10.96)	33 (32.35)
Employed	4 (13.79)	21 (28.77)	25 (24.51)
Financial Assistance (governmental grant)			
No	16 (51.61)	42 (56.76)	58 (55.24)
Yes	15 (48.39)	32 (43.24)	47 (44.67)
Type of Dwelling (current)			
Shack	10 (32.26)	6 (8.33)	16 (15.53)
Wendy house or backyard dwelling	1 (3.23)	10 (13.89)	11 (10.68)
House or flat	20 (64.52)	56 (77.78)	76 (73.79)
Living Area (current)			
Urban	8 (25.81)	69 (95.83)	77 (74.76)
Rural	9 (29.03)	3 (4.17)	12 (11.65)
Township	14 (45.16)	0 (0)	14 (13.59)
Composite SES quartiles			
Lowest	10 (34.38)	15 (21.13)	25 (25.00)
Low-moderate	8 (27.59)	16 (22.54)	24 (24.00)
Moderate-high	5 (17.24)	21 (29.58)	26 (26.00)
Highest	6 (20.69)	19 (26.76)	25 (25.00)

^a Due to rounding, totals may not add to 100%.

Table 5.2 Biomedical and reproductive risk factors

Variable	Number (%)	Mean (SD)
Biomedical risk factors		
Asthma	6 (5.7)	
Diabetes mellitus	6 (5.7)	
Pelvic inflammatory disease	6 (5.7)	
Cardiovascular disease	6 (5.7)	
Urinary tract infection	3 (2.9)	
Tuberculosis	1 (1.0)	
Hypertension	1 (1.0)	
Hyperemesis gravidarum	1 (1.0)	
Cumulative medical risk		
0	45 (42.86)	
1	51 (48.57)	
2	9 (8.57)	
Mean (SD)		0.66 (0.63)
Unplanned pregnancy	84 (80)	
Reproductive risk factors		
Female sex of infant (index)	48 (45.71)	
Nulliparity	43 (40.95)	
Prior caesarean section	19 (18.10)	
Prior LBW infant	16 (15.24)	
Prior premature birth	0 (0)	
Prior intra-uterine death	0 (0)	
Current multiple gestation	0 (0)	
Cumulative reproductive risk		
0	16 (15.24)	
1	56 (53.33)	
2	29 (27.62)	
3	4 (3.81)	
Mean (SD)		1.20 (0.74)

Table 5.3 Psychosocial symptoms and stressors

Variable	Number (%)			Mean (SD)
	MBK*	TCN**	Total	
IPV (adult)				
Past-year IPV (dichotomous)				
Emotional IPV	8 (25.81)	28 (38.36)	36 (34.62)	
Physical IPV	6 (20.00)	20 (27.03)	26 (25.00)	
Sexual IPV	0 (0)	7 (9.46)	7 (6.67)	
Lifetime IPV (dichotomous)				
Emotional IPV				
None	16 (51.61)	23 (31.08)	39 (37.14)	
Any Emotional IPV	15 (48.39)	51 (68.92)	66 (62.86)	
Once-off incident	3 (9.68)	11 (14.86)	14 (13.33)	
Low frequency	3 (9.68)	11 (14.86)	14 (13.33)	
Mid frequency	7 (22.58)	18 (24.32)	25 (23.81)	
High frequency	2 (6.45)	11 (14.86)	13 (12.38)	
Physical IPV				
None	20 (64.52)	29 (39.19)	49 (46.67)	
Any Physical IPV	11 (35.48)	45 (60.81)	56 (53.33)	
Once-off incident	3 (9.68)	9 (12.16)	12 (11.43)	
Low frequency	1 (3.23)	12 (16.22)	13 (12.38)	
Mid frequency	4 (12.90)	17 (22.97)	21 (20.00)	
High frequency	3 (9.68)	7 (9.46)	10 (9.52)	
Sexual IPV				
None	28 (90.32)	60 (81.08)	88 (83.81)	
Any Sexual IPV	3 (9.68)	14 (18.92)	17 (16.19)	
Once-off incident	1 (3.23)	5 (6.76)	6 (5.71)	
Low frequency	0 (0)	1 (1.35)	1 (0.95)	
Mid frequency	2 (6.45)	3 (4.05)	5 (4.76)	
High frequency	0 (0)	5 (6.76)	5 (4.76)	
Childhood trauma				
CTQ dichotomous – above threshold			39 (37.14)	
CTQ continuous				37.81 (14.47)
CTQ_emotional abuse (continuous)				8.65 (4.57)
CTQ_physical abuse (continuous)				7.16 (4.10)
CTQ_sexual abuse (continuous)				6.10 (3.78)
CTQ_emotional neglect (continuous)				8.86 (3.94)
CTQ_physical neglect (continuous)				7.04 (2.70)
Depression				
BDI-II (dichotomous – above threshold)			31 (29.52)	
BDI-II (continuous)				15.36 (9.99)
EPDS (dichotomous – above threshold)			28 (27.18)	
EPDS (continuous)				10.11 (5.51)
SRQ-20 (dichotomous – above threshold)			26 (24.76)	
SRQ-20 (continuous)				5.23 (4.05)
Posttraumatic stress disorder (PTSD)				
MPSS (dichotomous – above threshold)			23 (21.90)	

	Number (%)			Mean (SD)		
	MBK	TCN	Total	MBK	TCN	Total
Substance use						
Prenatal alcohol use (Dichotomous – above threshold)	2 (6.45)	11 (14.86)	13 (12.38)			
Prenatal alcohol use (Continuous)				1.97 (7.62)	3.28 (6.50)	2.90 (6.84)
Prenatal tobacco use (Dichotomous – above threshold)	1 (3.23)	44 (61.11)	45 (43.69)			
Prenatal tobacco use (Continuous)				0.74 (4.13)	13.29 (11.38)	9.51 (11.34)

*MBK Mbekweni
**TCN TC Newman

5.3.5 Infant outcomes

5.3.5.1 Anthropometry

A notable site-specific difference was evident in 6-month anthropometry. While the mean (SD) for weight for the total sample was 7.79 (SD = 1.26) kg, infants whose mothers had been recruited from TC Newman were found to have a lower mean (SD) weight of 7.57 (SD = 1.17) kg, when compared to those from Mbekweni [8.35 (1.38) kg], **Table 5.4**. When dichotomising WAZ scores at 6 months, it was found that the prevalence of decreased scores at TC Newman (8%) was far higher than at Mbekweni (0%). Head circumference (HC) did not follow this pattern. At 6 months, only a negligible difference in the mean (SD) of HC between sites was found, ie. [43.09 (2.82) cm] at Mbekweni; versus [43.35 (1.70) cm] at TC Newman. Further, the prevalence of decreased HCAZ scores at both clinics was approximately 3%. In total, 1 infant (1%) exhibited severe growth failure in weight from birth to 6 months; and 2 (2%) were found to have experienced severe growth failure in head circumference during this time period.

5.3.5.2 Developmental outcomes at age 6 months

Across all Bayley-III subtests, the mean scaled scores for each site and for the total study sample fell within the normal range, with no scores falling ≥ 1 SDs below the standardised mean of 10, **Table 5.4**. However, when dichotomising scaled scores, prevalence rates for developmental outcomes ≥ 1 SD below the mean ranged from 1% (certain adaptive behaviour subtests) to 22% (expressive communication). Notable site-specific differences in poor developmental outcomes (dichotomised) were also found across the Bayley-III scales (and their corresponding subtests). In almost all cases, the prevalence rates at TC Newman were found to be higher than at Mbekweni (eg. poor receptive communication outcomes: 21% at TC Newman compared to 10% at Mbekweni; poor gross motor outcomes: 14% at TC Newman versus 0% at Mbekweni; and poor socio-emotional outcomes: 11% at TC Newman compared to 4% at Mbekweni).

Table 5.4 Infant (6-month) anthropometry and indicators of developmental outcomes

Variable	Mbekweni	TC Newman	Total
Infant Anthropometry			
Mean weight in kg (SD)	8.35 (1.38)	7.57 (1.17)	7.79 (1.26)
Mean WAZ (SD)	0.76 (1.31)	-0.21 (1.23)	0.06 (1.34)
Low WAZ (WAZ of -2 or below) – <i>n</i> (%)	0 (0)	6 (8.33)	6 (5.94)
Mean head circumference in centimetres (SD)	43.09 (2.82)	43.35 (1.70)	43.28 (2.06)
Decreased head circumference for age – <i>n</i> (%)	1 (3.45)	2 (2.70)	3 (2.91)
Mean HCAZ (SD)	0.37 (2.01)	0.37 (1.26)	0.37 (1.50)
Low HCAZ (HCAZ of -2 or below) – <i>n</i> (%)	1 (3.45)	2 (2.70)	3 (2.91)
Severe growth failure (0-6 months) – weight – <i>n</i> (%)	0 (0)	1 (1.35)	1 (0.95)
Severe growth failure (0-6 months) – head circumference – <i>n</i> (%)	1 (3.45)	1 (1.35)	2 (1.94)
Infant Development			
Cognitive scale			
Mean score (SD)	9.55 (3.26)	9.00 (2.64)	9.16 (2.83)
Cognitive deficits – <i>n</i> (%)	4 (12.90)	7 (9.59)	11 (10.58)
Language (Communication) scale			
Receptive communication – mean score (SD)	9.35 (2.46)	9.33 (3.02)	9.34 (2.85)
Receptive communication deficits – <i>n</i> (%)	3 (9.68)	15 (20.55)	18 (17.31)
Expressive communication – mean score (SD)	10.48 (3.64)	9.41 (3.68)	9.73 (3.68)
Expressive communication deficits – <i>n</i> (%)	5 (16.13)	18 (24.66)	23 (22.12)
Motor scale			
Fine motor – mean score (SD)	13.29 (2.73)	11.64 (3.54)	12.13 (3.39)
Fine motor deficits – <i>n</i> (%)	1 (3.23)	6 (8.22)	7 (6.73)
Gross motor – mean score (SD)	10.94 (1.59)	10.08 (3.27)	10.34 (2.89)
Gross motor deficits – <i>n</i> (%)	0 (0)	10 (13.70)	10 (9.62)
Social-emotional scale			
Mean score (SD)	12.96 (3.01)	11.76 (3.66)	12.13 (3.50)
Social-emotional deficits – <i>n</i> (%)	1 (4.17)	6 (10.91)	7 (8.86)
Adaptive behavior scale			
Communication – mean score (SD)	10.55 (1.75)	10.51 (2.10)	10.52 (1.99)
Communication deficits – <i>n</i> (%)	0 (0)	1 (1.35)	1 (0.95)
Health and safety – mean score (SD)	9.58 (0.72)	9.64 (0.96)	9.62 (0.89)
Health and safety deficits – <i>n</i> (%)	0 (0)	1 (1.35)	1 (0.95)
Leisure – mean score (SD)	10.16 (2.33)	10.59 (2.17)	10.47 (2.21)
Leisure deficits – <i>n</i> (%)	1 (3.23)	5 (6.76)	6 (5.71)
Self-care – mean score (SD)	9.90 (1.83)	10.27 (1.75)	10.16 (1.77)
Self-care deficits – <i>n</i> (%)	1 (3.23)	3 (4.05)	4 (3.81)
Self-direction – mean score (SD)	9.48 (1.93)	9.42 (2.20)	9.44 (2.11)
Self-direction deficits – <i>n</i> (%)	3 (9.68)	8 (10.81)	11 (10.48)
Social – mean score (SD)	11.58 (1.15)	11.78 (1.64)	11.72 (1.51)
Social deficits – <i>n</i> (%)	0 (0)	1 (1.35)	1 (0.95)
Motor – mean score (SD)	10.39 (2.01)	10.09 (2.21)	10.18 (2.15)
Motor deficits – <i>n</i> (%)	2 (6.45)	4 (5.41)	6 (5.71)

5.3.6 Associations between psychiatric symptoms and stressors during pregnancy and poor infant developmental outcomes at age 6 months

5.3.6.1 Bivariate correlation analyses

A number of statistically significant correlations were found, as described below, **Table 5.5**. When considering maternal sociodemographic variables, it was found that unmarried women were more likely to deliver infants with poor fine motor outcomes at age 6 months ($r = -0.20$; $p = 0.037$). Maternal psychiatric symptoms and stressors also emerged as an important variable in the correlation analyses. Depression during pregnancy (as measured by the EPDS), was found to be associated with poor infant developmental outcomes in the adaptive behaviour (motor) subtest ($r = -0.21$; $p = 0.037$). Infants of mothers who had been exposed to IPV were more likely to experience a range of poor developmental outcomes. For example, mothers reporting a lifetime history of emotional abuse were at increased risk of delivering infants with poor outcomes in the receptive communication (language) ($r = -0.27$; $p = 0.005$) subtest; those with a lifetime history of physical IPV were more likely to deliver infants with poor outcomes in receptive communication (language) ($r = -0.20$; $p = 0.04$) and in the adaptive behaviour (motor) delay ($r = -0.20$; $p = 0.04$) subtests at 6 months; and those exposed to sexual IPV in their lifetimes were at increased risk of delivering infants with subsequently poor fine motor outcomes ($r = -0.21$; $p = 0.03$). Unsurprisingly, maternal exposure to recent (past-year) IPV was also found to be significantly associated with poor infant developmental outcomes. Following the risk profile of lifetime emotional abuse, mothers who reported emotional IPV during the past year were more likely to deliver infants with poor outcomes in the receptive communication (language) ($r = -0.24$; $p = 0.01$) and adaptive behaviour (motor) subtests ($r = -0.19$; $p = 0.0498$) at age 6 months. Further, those reporting past-year physical IPV were at increased risk of delivering infants with poor expressive communication (language) outcomes ($r = 0.25$; $p = 0.01$); while past-year exposure to sexual IPV was found to be significantly associated with poor fine motor outcomes ($r = -0.30$; $p = 0.002$) at infant age 6 months.

Infants whose mothers had used substances during pregnancy were more likely to experience poor developmental outcomes at age 6 months, as measured by a range of Bayley-III scales.

For example, maternal alcohol use was significantly associated with poor developmental outcomes in the communication subtest of the adaptive behaviour scale ($r = -0.19$; $p = 0.048$). Further, tobacco use was found to be associated with poor expressive communication outcomes ($r = -0.22$; $p = 0.027$). In terms of infant growth and growth velocity, those with decreased HCAZ scores at 6 months were more likely to experience poor receptive communication (language) outcomes ($r = 0.20$; $p = 0.049$). Further, those with reduced growth in head circumference for the first six months of life were at increased risk of poorer socio-emotional developmental outcomes ($r = -0.26$; $p = 0.023$).

5.3.6.2 Multiple regression analyses

In the final regression analyses, outcomes of interest were poor developmental outcomes in any of the Bayley-III scales and subtests, ie. cognitive; gross motor; fine motor; receptive communication; expressive communication; socio-emotional; and the adaptive behaviour subtests – communication, health and safety, leisure, self-care, self-direction, social and motor. Predictor variables were those pertaining to maternal sociodemographic variables, general medical and psychiatric risk profiles, and alcohol or substance use.

The regression model predicting fine motor development reached significance [$r^2 = 0.20$ (adjusted $r^2 = 0.13$, $F(8,88) = 2.75$, $p = 0.0094$] (**see Table 5.6**), with maternal exposure to past-year sexual IPV [$t = -2.86$, $p = 0.005$], and alcohol use during pregnancy [$t = -2.29$, $p = 0.02$] each found to be significant for predicting poor outcome in infant fine motor development at age 6 months, when controlling for study site (clinic), maternal marital status, SES, depression, PTSD and tobacco use.

Table 5.5 Bivariate analyses of the correlation between a number of psychosocial stressors, symptoms and other risk factors, and measures of infant (6-month) developmental outcomes

Pearson correlation coefficients

Prob > |r| under H0: Rho = 0

Number of Observations

	Sociodemographics			General Medical Health		Planning of Birth/ Partner Support	
	Age	Marital status	Income	Biomedical Health	Reproductive Health	Pregnancy intention	Partner Support
COGNITIVE	-0.03442 0.7287 104	-0.14948 0.1299 104	-0.01040 0.9174 102	0.10734 0.2781 104	0.12874 0.1928 104	-0.03767 0.7042 104	-0.05972 0.5471 104
REC_COMM	-0.00906 0.9273 104	-0.03718 0.7079 104	-0.11499 0.2498 102	0.03279 0.7410 104	0.11193 0.2580 104	-0.01745 0.8604 104	0.18535 0.0596 104
EXP_COMM	0.17663 0.0729 104	0.13466 0.1729 104	-0.01204 0.9044 102	0.19227 0.0505 104	0.04780 0.6299 104	-0.03495 0.7247 104	-0.06842 0.4901 104
FINE MOTOR	-0.05183 0.6013 104	-0.20475 0.0371** 104	-0.04805 0.6316 102	0.17516 0.0753 104	0.05936 0.5494 104	-0.12655 0.2005 104	-0.06549 0.5089 104
GROSS MOTOR	0.09581 0.3333 104	-0.05819 0.5574 104	0.12410 0.2140 102	0.14865 0.1321 104	0.05579 0.5738 104	-0.02553 0.7970 104	-0.01893 0.8487 104
SOC_EMO	-0.03018 0.7918 79	0.05053 0.6583 79	-0.14729 0.1952 79	0.05731 0.6159 79	-0.01360 0.9053 79	-0.11653 0.3064 79	0.00023 0.9984 79
AB_COMM	0.07688 0.4357 105	0.07988 0.4179 105	-0.01195 0.9046 103	0.12101 0.2188 105	-0.07189 0.4661 105	0.02403 0.8077 105	-0.06887 0.4851 105
AB_HS	-0.17402 0.0758 105	-0.17166 0.0800 105	0.02538 0.7991 103	0.03893 0.6934 105	0.04376 0.6576 105	0.08045 0.4146 105	-0.05076 0.6071 105
AB_LS	0.01901 0.8473 105	0.02420 0.8064 105	-0.01225 0.9022 103	-0.00823 0.9336 105	0.20091 0.0399** 105	-0.03025 0.7594 105	0.04947 0.6162 105
AB_SC	-0.09214 0.3499 105	-0.00399 0.9678 105	0.09278 0.3512 103	-0.01863 0.8504 105	0.01175 0.9053 105	-0.00540 0.9564 105	0.04014 0.6843 105
AB_SD	-0.06400 0.5166 105	-0.04351 0.6595 105	0.01902 0.8488 103	0.12065 0.2202 105	-0.00739 0.9403 105	0.03172 0.7481 105	0.15992 0.1032 105
AB_Soc	-0.13453 0.1712 105	-0.02575 0.7943 105	0.10976 0.2697 103	0.01064 0.9142 105	0.14480 0.1405 105	0.09192 0.3510 105	0.13091 0.1832 105
AB_MO	-0.13711 0.1631 105	-0.12452 0.2057 105	0.02904 0.7709 103	0.14514 0.1396 105	0.09816 0.3192 105	-0.10918 0.2676 105	0.03608 0.7148 105

Pearson correlation coefficients

Prob > |r| under H0: Rho = 0

Number of Observations

	Psychosocial Symptoms & Stressors				
	Depression			PTSD	Childhood Trauma
	BDI-II	EPDS	SRQ		
COGNITIVE	0.00866	0.09208	0.02008	-0.18040	0.06966
	0.9305	0.3574	0.8397	0.0669	0.4822
	104	102	104	104	104
REC_COMM	-0.10343	-0.07712	-0.07198	-0.16931	0.06698
	0.2961	0.4410	0.4678	0.0858	0.4993
	104	102	104	104	104
EXP_COMM	0.05558	0.12175	0.02794	-0.05190	-0.03860
	0.5752	0.2228	0.7783	0.6008	0.6972
	104	102	104	104	104
FINE MOTOR	-0.05666	0.02501	-0.12778	-0.09742	-0.10000
	0.5678	0.8030	0.1961	0.3252	0.3125
	104	102	104	104	104
GROSS MOTOR	-0.00026	-0.01805	0.04173	-0.19148	0.02671
	0.9980	0.8571	0.6741	0.0515	0.7878
	104	102	104	104	104
SOC_EMO	0.05661	-0.01205	-0.01504	-0.10569	-0.03124
	0.6202	0.9172	0.8954	0.3539	0.7846
	79	77	79	79	79
AB_COMM	-0.02123	-0.02411	0.08169	-0.08191	-0.04490
	0.8298	0.8090	0.4074	0.4062	0.6492
	105	103	105	105	105
AB_HS	0.02749	0.05034	0.03501	0.12351	-0.18966
	0.7807	0.6136	0.7229	0.2094	0.0526
	105	103	105	105	105
AB_LS	-0.05856	0.05802	0.10172	-0.02855	0.04931
	0.5529	0.5604	0.3018	0.7725	0.6174
	105	103	105	105	105
AB_SC	-0.00552	-0.00597	0.06724	-0.08783	0.00909
	0.9555	0.9523	0.4955	0.3729	0.9266
	105	103	105	105	105
AB_SD	-0.18807	-0.11427	-0.02421	-0.04466	-0.01392
	0.0547	0.2504	0.8063	0.6510	0.8879
	105	103	105	105	105
AB_Soc	-0.10681	-0.07030	-0.00058	0.12802	-0.02532
	0.2782	0.4804	0.9953	0.1931	0.7976
	105	103	105	105	105
AB_MO	-0.19045	-0.20640	-0.07232	-0.08794	-0.17898
	0.0517	0.0365**	0.4635	0.3724	0.0677
	105	103	105	105	105

Pearson correlation coefficients

Prob > |r| under H0: Rho = 0

Number of Observations

	Psychosocial Symptoms & Stressors					
	Emotional IPV (lifetime)	Physical IPV (lifetime)	Sexual IPV (lifetime)	Emotional IPV (past-year)	Physical IPV (past-year)	Sexual IPV (past-year)
COGNITIVE	0.03182 0.7484 104	-0.00713 0.9428 104	-0.10869 0.2721 104	0.02095 0.8336 103	0.00117 0.9906 103	-0.19258 0.0502 104
REC_COMM	-0.27227 0.0052** 104	-0.20281 0.0389** 104	-0.07385 0.4562 104	-0.24370 0.0131** 103	-0.15923 0.1082 103	-0.14007 0.1561 104
EXP_COMM	-0.00141 0.9886 104	-0.01291 0.8965 104	0.16178 0.1008 104	0.13152 0.1854 103	0.24543 0.0125** 103	0.03021 0.7608 104
FINE MOTOR	-0.04483 0.6513 104	-0.05664 0.5679 104	-0.20830 0.0338** 104	-0.06157 0.5367 103	0.01738 0.8617 103	-0.29505 0.0024** 104
GROSS MOTOR	-0.00109 0.9912 104	-0.03712 0.7083 104	0.02497 0.8014 104	-0.08066 0.4180 103	0.02936 0.7685 103	-0.12477 0.2070 104
SOC_EMO	-0.10242 0.3691 79	0.01786 0.8758 79	-0.01386 0.9035 79	-0.08134 0.4790 78	0.11792 0.3038 78	-0.16163 0.1547 79
AB_COMM	-0.05036 0.6099 105	0.00928 0.9252 105	0.00374 0.9698 105	-0.09957 0.3146 104	0.01957 0.8437 104	-0.03212 0.7450 105
AB_HS	-0.00409 0.9670 105	-0.07040 0.4754 105	-0.09841 0.3179 105	-0.09420 0.3415 104	-0.12457 0.2077 104	-0.01433 0.8846 105
AB_LS	-0.06280 0.5245 105	-0.08348 0.3972 105	-0.07243 0.4628 105	-0.10005 0.3122 104	0.00502 0.9596 104	-0.02194 0.8242 105
AB_SC	0.00628 0.9493 105	-0.05611 0.5697 105	0.00386 0.9688 105	0.01248 0.8999 104	0.11682 0.2376 104	-0.02455 0.8037 105
AB_SD	-0.00708 0.9429 105	-0.00254 0.9795 105	-0.10090 0.3058 105	0.04224 0.6703 104	0.01054 0.9154 104	-0.09204 0.3504 105
AB_Soc	-0.09684 0.3257 105	-0.12652 0.1984 105	-0.01991 0.8402 105	-0.12919 0.1912 104	-0.01473 0.8820 104	-0.00169 0.9863 105
AB_MO	-0.19083 0.0512 105	-0.19836 0.0425** 105	-0.08717 0.3766 105	-0.19291 0.0498** 104	-0.01552 0.8757 104	-0.09409 0.3397 105

Pearson correlation coefficients

Prob > |r| under H0: Rho = 0

Number of Observations

	Substance Use		Infant (6 month) Anthropometry		Growth Velocity (z-scores)	
	Tobacco	Alcohol	WAZ_6 months	HCAZ_6 months	WAZ_velocity	HCAZ_velocity
COGNITIVE	-0.18732	0.06306	0.00856	0.00543	-0.16309	-0.11938
	0.0594	0.5248	0.9313	0.9568	0.0981	0.2321
	102	104	104	102	104	102
REC_COMM	-0.12516	-0.06364	0.07856	0.19533	-0.17535	0.04534
	0.2100	0.5210	0.4280	0.0491**	0.0750	0.6509
	102	104	104	102	104	102
EXP_COMM	-0.21874	0.05102	0.11086	-0.01116	-0.03425	-0.04481
	0.0272**	0.6070	0.2626	0.9113	0.7300	0.6547
	102	104	104	102	104	102
FINE MOTOR	-0.13974	-0.18514	0.14836	0.10464	-0.09481	-0.07926
	0.1613	0.0599	0.1328	0.2952	0.3384	0.4285
	102	104	104	102	104	102
GROSS MOTOR	-0.07583	-0.07937	0.15180	0.02448	-0.03962	-0.15727
	0.4487	0.4232	0.1240	0.8071	0.6897	0.1144
	102	104	104	102	104	102
SOC_EMO	-0.19894	0.01711	0.15873	-0.11339	0.04834	-0.25694
	0.0828	0.8810	0.1623	0.3229	0.6723	0.0232**
	77	79	79	78	79	78
AB_COMM	-0.15050	-0.19368	0.18794	0.08549	-0.07266	-0.13354
	0.1292	0.0477**	0.0549	0.3906	0.4614	0.1787
	103	105	105	103	105	103
AB_HS	-0.01386	-0.14531	0.01378	0.18647	0.13074	0.18988
	0.8895	0.1391	0.8890	0.0593	0.1837	0.0547
	103	105	105	103	105	103
AB_LS	-0.03767	-0.05642	-0.08590	0.01769	-0.18478	-0.02561
	0.7056	0.5676	0.3836	0.8592	0.0592	0.7973
	103	105	105	103	105	103
AB_SC	-0.00537	0.05063	0.03849	-0.04673	-0.11105	-0.10540
	0.9571	0.6080	0.6967	0.6393	0.2594	0.2893
	103	105	105	103	105	103
AB_SD	-0.07185	-0.07868	0.02422	0.07752	0.00069	0.09597
	0.4708	0.4250	0.8063	0.4364	0.9944	0.3349
	103	105	105	103	105	103
AB_Soc	0.02887	-0.18352	0.03868	0.15965	-0.04850	0.07389
	0.7722	0.0609	0.6952	0.1072	0.6232	0.4582
	103	105	105	103	105	103
AB_MO	-0.02717	-0.15911	0.18973	0.17822	-0.15412	-0.11782
	0.7853	0.1050	0.0526	0.0717	0.1165	0.2359
	103	105	105	103	105	103

**p < 0.05

<i>REC_COMM</i>	<i>Receptive Communication</i>
<i>EXP_COMM</i>	<i>Expressive Communication</i>
<i>SOC_EMO</i>	<i>Socio-Emotional</i>
<i>AB_COMM</i>	<i>Adaptive Behaviour – Communication</i>
<i>AB_HS</i>	<i>Adaptive Behaviour – Health & Safety</i>
<i>AB_LS</i>	<i>Adaptive Behaviour – Leisure</i>
<i>AB_SC</i>	<i>Adaptive Behaviour – Self-Care</i>
<i>AB_SD</i>	<i>Adaptive Behaviour – Self-Direction</i>
<i>AB_Soc</i>	<i>Adaptive Behaviour – Social</i>
<i>AB_MO</i>	<i>Adaptive Behaviour – Motor</i>

Table 5.6 Multiple linear regression analyses of the association between exposure to past-year sexual IPV, and poor infant developmental (fine motor) outcomes

	B (SE)
IPV (sexual, past-year)	-4.265 (1.490)**
Alcohol	-0.111 (0.048)**
Study site (Mbekweni)	0.987 (0.921)
Marital status (married)	-0.192 (0.751)
Socioeconomic status	0.127 (0.157)
Depression (EPDS)	0.107 (0.064)
PTSD	-0.745 (0.855)
Tobacco	-0.007 (0.035)

** $p < 0.05$

5.4 Discussion and conclusions

In this study of infant neurodevelopmental outcomes in a LMIC population, we found that, although the Bayley-III mean scaled scores were within the “normal” range, there was a clinic-specific difference across all Bayley-III subtests; and maternal exposure to past-year sexual IPV and alcohol use during pregnancy were found each to be significantly associated with poor fine motor development at infant age 6 months, when controlling for a number of potential confounders.

As with the developmental markers in this infant cohort, measures of weight-for-age and head-circumference-for-age were found to be within the normal range according to the WHO child growth standards (WHO 2014); and only a negligible percentage of the study sample exhibited severe failure in growth from birth to 6 months of age. This is in contrast to the findings of the two Lancet series reporting loss of developmental potential of young children in LMIC countries (Grantham-McGregor et al. 2007; Walker et al. 2007, 2011; Engle et al. 2007, 2011; Lake 2011); and evidence from the recent WHO/UNICEF report on country, regional and global estimates (UNICEF & WHO 2004), which indicated an estimated prevalence of LBW of 14% in Sub-Saharan Africa. However, our study population may be educated better than some in South Africa, as evidenced by the data that most had some high school education (Walker et al. 2011; Boyle et al. 2006). Further, pre- and postnatal care for mothers enrolled in the DCHS is at least a minimal level, with exposure to longitudinal health promotive strategies (such as breastfeeding in this age group).

When dichotomising the scaled scores, a site-specific difference across all Bayley-III scales was noted, with the prevalence of poor developmental outcomes at TC Newman generally higher than at Mbekweni. Further, measures of anthropometry at 6 months also differed across the two sites, with participants at TC Newman fairing more poorly across most indicators (including decreased WAZ scores) than those at Mbekweni. This discrepancy may be related to the notable difference in risk-factor profile between sites, with past-year IPV exposure, tobacco use during pregnancy and prenatal alcohol consumption all emerging as more prevalent at TC Newman.

A statistically significant association between past-year maternal exposure to sexual IPV and poor fine motor outcomes in infancy was demonstrated. IPV exposure during pregnancy is exceedingly high in South Africa, with prevalence rates ranging from 2% to 57% (meta-analysis yielding an overall prevalence of 15%) (Shamu et al. 2011). Adverse outcomes of such exposure may include maternal *sequelae* such as pregnancy loss, inadequate weight gain, depression and PTSD (Taillieu & Brownridge 2010; Martin et al. 2006; Rodriguez et al. 2008); as well as birth-related effects such as preterm labour/delivery and low birthweight (see *Chapter 4 – Publication 2, p 42-72*; and Taillieu & Brownridge 2010; Covington et al. 2001; Murphy et al. 2001). However, data on the association between IPV exposure during pregnancy and developmental outcomes currently are limited. To the best of our knowledge, ours is the first study to find this association. Given the high prevalence of IPV, and the known birth-related adverse effects of this stressor, further work to delineate outcomes in early child neurodevelopment would be warranted.

Maternal alcohol use during pregnancy was found to be significantly associated with poorer fine motor developmental outcomes at infant age 6 months. Despite the paucity of data in LMIC settings, this finding is in keeping with the large body of work on the adverse effects of prenatal alcohol consumption (eg. Mattson et al. 2010, 2011, 2013). As was the case in our study sample, most studies to date of fine and gross motor development suggest an adverse effect of prenatal alcohol exposure (Jones et al. 1973; Kyllerman et al. 1985; Barr et al. 1990; Mattson & Riley 1998).

Notably, no significant associations were demonstrated between risk factors such as maternal psychological distress, psychopathology (PTSD, depression) or cigarette smoking; and poor infant development in this study sample. While there is a paucity of existing data on the effect of maternal PTSD on infant neurodevelopment (see *Chapter 6, Section 6.4 – Discussion and conclusions, p 113*), a number of prospective, longitudinal maternal-child cohort studies have found that children exposed to maternal stress, depression and anxiety during the prenatal period are at increased risk of impaired cognitive development (eg. see Bergman et al. 2007; Deave et al. 2008). Maternal smoking during pregnancy has also been shown to have a

deleterious effect on child neurodevelopment (eg. Huizink & Mulder 2007), likely due to foetal hypoxia and altered brain development (Cole et al. 1972).

We also failed to demonstrate a statistically significant relationship between most infant growth parameters and neurodevelopmental outcomes (although - consistent with the relationship between anthropometry and infant development - infants in our cohort with reduced HCAZ scores and those with impaired growth in head circumference during the first six months of life, also had poor developmental outcomes). The discrepancy between our findings and prior work in this field may be attributed to the overall 'normal' growth of the study cohort. Further, developmental testing at this early age may not allow for the detection of more subtle effects and associations.

An immediate question is how maternal IPV exposure, prenatal alcohol consumption and other psychiatric symptoms and stressors contribute to poorer outcomes in infant development. In general, these effects may be exerted via direct or indirect mechanisms. For example, direct effects of alcohol use during pregnancy include teratogenicity (effects on primary structural development) on the foetal brain, and subtler alterations in brain growth, maturation, neurotransmitter concentration and neural pathway development (Donald 2013). Indirect effects may be neurobiological (due to placental insufficiency) or environmental, relating to the overall burden of harm of alcohol consumption or IPV exposure. Environmental factors such as occupational instability, malnutrition, poor health-seeking behaviour, sexual risk-taking behaviour, and concomitant tobacco and drug use may be associated with alcohol misuse and other psychiatric symptoms and stressors during pregnancy and may compound thus the adverse effect on childhood developmental outcomes (O'Connor et al. 2011; Harker et al. 2008).

The current study is limited by a number of factors. First, this is a cross-sectional analysis of a longitudinal birth cohort data set. Thus, temporality of causation is inherently difficult to determine. Second, most of the maternal data included in the analyses were self-reported. Thus, intentional or unintentional under-reporting may have introduced bias into the assessment of IPV exposure, alcohol use and other predictor variables. In future, the inclusion

of objective and quantitative measures of substance use (eg. fingernails and/or hair samples) may be of help in countering such self-report bias and epidemiological underestimation. Third, all data were collected from one sub-district in the Western Cape Province, South Africa. Thus, national and international generalisability is limited. Fourth, our sample size is relatively small, with reduced statistical power to detect small associations. Fifth, while unmeasured and residual confounding is likely in studies such as these, we attempted to minimise this by adjusting for key confounding variables such as SES and study site. Finally, although the inclusion of a large number of bivariate correlation analyses (**see Table 5.5**) may have increased the potential for Type I error (and the detection of some false positives), these correlations were intended to be exploratory; and to inform the final multiple regression model predicting poor fine motor infant developmental outcomes (**Table 5.6**). Nonetheless, in light of the potential of false positives, our key findings of a significant association each between past-year sexual IPV and prenatal alcohol use; and poor fine motor outcomes in infancy, should be taken with caution.

Despite these limitations, our study provides valuable proof-of-principle preliminary data, complementing the emerging South African evidence base. Further, ours is a novel exploratory study in a number of notable ways. First, as it is nested within a much larger longitudinal birth cohort, the maternal and infant dataset contains a range of physical measures. Second, the study population is high-risk, with several psychiatric symptoms and stressors. Third, in this study, infants were assigned to the “exposed”-to-alcohol category at any reported level of maternal alcohol intake during pregnancy; they were not classified according to foetal alcohol spectrum disorder (FASD) clinical diagnostic criteria. Thus, our findings underscore the adverse effect of any amount of alcohol exposure in utero, which remains after controlling for associated risk factors (see also Testa et al. 2003). Fourth, while the detrimental effects of prenatal alcohol exposure have been well-described in this paper and elsewhere, additional psychiatric risk factors during pregnancy rarely are explored in LMIC populations. In fact, to the best of our knowledge, ours is the first study to examine the association between IPV exposure during pregnancy and child neurodevelopmental outcomes. Thus, further investigation of the multiple and interrelated prenatal risk factors for poor infant development is warranted.

Finally, our infant population is very young, and thus at an age at which subtle manifestations of effects on development may be difficult to detect. In light of this, our finding of a statistically significant association each between IPV exposure and prenatal alcohol consumption, and poor outcome in infant fine motor development, is noteworthy.

Primary prevention of the neurodevelopmental *sequelae* of prenatal IPV exposure, alcohol consumption and other psychiatric symptoms and stressors should be the initial goal of intervention strategies. Health education for all women of child-bearing age is essential in this regard. Secondary preventative strategies in LMIC countries are most likely to be effective if they are targeted at identifying children at risk early. Detecting poor developmental outcomes at this early age using sensitive measures (such as the Bayley-III) may be useful in planning and implementing appropriate interventions during the so-called “window of sensitivity” in the first months of life (Morgan 2013). Recommendations for effective early intervention strategies have included aiming these at children of lower SES; implementing for a longer period of time; ensuring high quality and high intensity; integrating with contextual variables such as family support, nutrition and educational networks; facilitating cost-effectiveness; and providing learning and skill-building experiences to children and families (Engle et al. 2007). Continued research in this field is essential to inform interventions aimed at reducing the developmental losses affecting children in the LMIC context. Through understanding of the magnitude and extent of this problem, appropriate preventative and intervention strategies ultimately may be devised.

The next chapter – based on *Publication 4* – will discuss the association between maternal PTSD and poor infant neurodevelopment at age 6 months in this cohort, thus addressing the fourth research objective of this thesis.

CHAPTER 6

PUBLICATION 4

Maternal posttraumatic stress disorder and infant developmental outcomes in the Drakenstein Child Health Study

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Synopsis

As a complement to *Chapter 5 – Publication 3 (p 73-99)*, this chapter will focus on the association between maternal PTSD and infant developmental outcomes in the DCHS cohort, thus assessing directly the fourth research objective of this thesis (*see Chapter 1, Section 1.6 – Study objectives and related publications, p 7*):

To determine the association between maternal PTSD and poor infant neurodevelopment at age 6 months in the study cohort.

This chapter is based on a manuscript that has been submitted to the *British Journal of Psychiatry (BJ Psychiatry)*, as we believe it will be of great interest to the core readership of this journal, ie. practising psychiatrists, many of whom may be working in a LMIC setting such as South Africa.

Abstract

Background

Maternal PTSD may affect infant neurodevelopment adversely in LMIC settings. We investigated the association between maternal PTSD and infant development in the DCHS.

Method

Maternal psychopathology was assessed using self-report and clinician-administered interviews; and 6-month infant development using the Bayley Scales of Infant and Toddler Development. Linear regression analyses explored associations between predictor and outcome variables.

Results

Data from 111 mothers and 112 infants (one set of twins) were included. Most mothers (72%) reported lifetime trauma exposure; the lifetime prevalence of PTSD was 20%. Maternal PTSD was significantly associated with poorer fine motor and adaptive behaviour (motor) development, with the latter remaining significant when adjusted for site, alcohol dependence, and birth HCAZ score.

Conclusion

Preliminary findings suggest that maternal PTSD may impair infant neurodevelopment. Further work in LMIC populations may improve early childhood development in this context.

Keywords: PTSD, pregnancy, intergenerational, infant neurodevelopment, South Africa

6.1 Introduction

PTSD is a debilitating disorder affecting vulnerable individuals who have been exposed to traumatic events. Gender-specific differences in trauma exposure, and in the phenomenology of PTSD, have been well-documented (Herman et al. 2009; Kessler et al. 1995; Sartor et al. 2011; Olff et al. 2007), with females at overall greater risk. The development of PTSD during the prenatal and peripartum periods may be particularly harmful, with potential adverse effects on both mother and child (Seng et al. 2011; Morland et al. 2007; Rogal et al. 2007). There is a growing body of work documenting the detrimental effects of trauma exposure and PTSD during pregnancy. For example, in their prospective study of 89 five-and-a-half year-old offspring of mothers exposed to a moderately severe natural disaster, Laplante and colleagues (2008) reported that children exposed to high levels of objective stressors in utero scored lower on measures of cognitive and language abilities, compared to those who had been exposed to low-moderate levels of prenatal stress. However, there is a relative paucity of research emerging from LMIC settings. Further, few studies to date have explored specifically the association between maternal trauma exposure or PTSD and infant neurodevelopmental outcomes.

The DCHS provides a unique opportunity to investigate the association between maternal trauma and PTSD with adverse birth and developmental outcomes in infancy and childhood in a previously understudied population (see Zar et al. 2015). Prior studies in this birth cohort (eg. Koen et al. 2014) have found that this population has a higher prevalence of PTSD than has been reported in studies such as the SASH (Williams et al. 2007). The purpose of the current analysis was to examine the association between maternal PTSD and infant development at age 6 months; we hypothesised that PTSD would affect adversely infant developmental outcomes in this study sample.

6.2 Methods

Data from the DCHS were used in this investigation of the association between maternal PTSD and infant neurodevelopment in a South African community setting. This analysis includes a sub-sample of mothers enrolled into the cohort between March 2012 and December 2013. Details of participant enrollment can be found in *Chapter 2, Section 2.3 – Participant recruitment and follow-up (p 9-10)*; and ethical processes relevant to this study in *Chapter 2, Section 2.5 – Ethical considerations (p 20-21)*.

6.2.1 Measures

All assessment tools have been described in detail in *Chapter 2, Section 2.4 – Measures and variable calculations (p 10-20)*. For the purposes of this analysis, data pertaining to specific variables were collected as follows:

Maternal assessment

- a) **Sociodemographic characteristics** – using the SES questionnaire designed for the DCHS.
- b) **Psychosocial risk factors** – using the World Mental Health Life Events Questionnaire (adapted from Myer et al. 2008), the Beck Depression Inventory (BDI-II) (Beck et al. 1961, 1988, 1996a,b), the Edinburgh Postnatal Depression Rating Scale (EPDS) (Cox et al. 1987), the SRQ-20 (Harding et al. 1980; Scholte et al. 2011) and the WHO’s Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (WHO ASSIST Working Group 2002).
- c) **Trauma exposure and PTSD** – using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1994), the Intimate Partner Violence (IPV) Questionnaire (Jewkes 2002; Shamu et al. 2011), and the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al. 1997; Sheehan et al. 1997, 1998). For the purposes of this study, maternal phenotype data from the 6-month postpartum MINI assessment were used.

On completion of the assessment, those participants with suspected psychopathology (including PTSD, depression and/or substance use) were referred by study staff to the most

appropriate care providers in the community, according to a standard operating procedure devised for the purposes of this study. Further, information leaflets designed by the study team were made available to all participants to facilitate autonomous accessing of local health services.

Infant outcomes

Anthropometry (weight, HC, length/height) at birth and 6 months was measured by trained clinical staff, and the relevant z-scores then were calculated using the Fenton preterm growth chart as described in *Chapter 2, Section 2.4 – Measures and variable calculation (p 18)*. Infant developmental outcomes at age 6 months were assessed with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) – see also *Chapter 2, Section 2.4 (p 19-20)*. The present analysis included only live births, and infants were included if they had developmental data from the 6-month postpartum visit.

6.2.2 Statistical analyses

All data were analysed using *Stata 12* (StataCorp Inc, College Station, Texas, USA). Frequency distributions and medians (interquartile ranges) were used to describe sociodemographic variables of interest (maternal age, marital status, education, employment, income); childhood and adult trauma exposure and stressful life events; PTSD, depression and psychological distress; alcohol and substance use; birth and 6-month anthropometry; and infant developmental outcomes. Among trauma-exposed mothers, crude associations between maternal PTSD and infant development at age 6 months were explored using two-sample t-tests and Wilcoxon rank sum tests (Mann-Whitney tests) for normally and non-normally distributed outcome variables, respectively, where the outcome of interest was scaled scores on each subtest of the Bayley-III. In cases where PTSD was significantly associated with scaled scores on the Bayley-III subtests in exploratory bivariate analysis (at $p < 0.05$), linear regression models were used to investigate the associations between maternal PTSD, potential confounders, and infant developmental outcomes. The potential confounders explored included recruitment site, maternal education, IPV, maternal alcohol use, and infant

anthropometry. This selection was informed by acyclic graphs and models built prior to conducting the analyses. Likelihood ratio tests were used to assess model fit. These analyses were restricted to trauma-exposed mothers in order better to parse out the effects of PTSD itself on infant development.

6.3 Results

6.3.1 Maternal sociodemographic characteristics

A total of 734 mothers were enrolled during this study period. Of these, 50 mothers were lost to follow-up between enrollment and delivery, and 10 experienced pregnancy losses (miscarriage or stillbirth). Thus, there were 675 live births (including one set of twins) during this period. Those without completed antenatal (maternal) and postnatal (infant developmental and maternal MINI assessment) data at the time of the study were excluded from the present analysis. Data from 111 mothers and 112 infants (including one set of twins) were included in the final analysis.

The median age of mothers at enrollment was approximately 25 years, **Table 6.1**. Most (62%) were unmarried, and almost a third (32%) were primigravid. The prevalence of maternal HIV infection was 19%. Despite most participants (62%) having completed some secondary education, unemployment in this study sample was highly prevalent (84%). The vast majority (88%) reported a household income of less than R5,000 per month.

6.3.2 Psychosocial risk factors

More than a quarter of the study sample scored above threshold on the self-report measures of depression (BDI-II: 29%; EPDS: 26%), **Table 6.1**. These findings were supported by the clinician-administered psychiatric assessment (MINI), in which 20% of the study sample was found to have experienced a major depressive episode (lifetime). Approximately a quarter (24%) reported experiencing psychological distress (as measured by the SRQ-20), despite a relatively low median (IQR) score (1 (0; 3)) on the measure of past-year stressful life events. Tobacco and alcohol use was prevalent in this study sample, with 41% reporting lifetime use of each of these

substances. Further, almost a third (30%) of study participants reported tobacco use during pregnancy, with 8% reporting alcohol consumption during this period. Clinician-administered assessment yielded a sample prevalence of 13% for lifetime alcohol abuse or dependence.

6.3.3 Trauma exposure and PTSD

Approximately a third (30%) of the study sample reported exposure to trauma during childhood, with half having been exposed to IPV during their lifetimes, **Table 6.1**. Further, more than a third (35%) had experienced IPV during the past year. The majority (72%) of this study sample reported exposure to at least one lifetime traumatic event (as defined by the DSM-5) – including, but not limited to, childhood trauma and IPV. The overall lifetime prevalence of PTSD was 20%.

Table 6.1 Maternal sociodemographic, psychosocial characteristics, trauma exposure and PTSD

Variable	Mbekweni n (%)	TC Newman n (%)	Total n (%)
Number of mothers	56 (50)	55 (50)	111
DEMOGRAPHIC AND PSYCHOSOCIAL CHARACTERISTICS			
<i>Self-reported demographic and psychosocial characteristics (antenatal study visit)</i>			
Ethnicity			
Black/African	55 (98)	0 (0)	55 (50)
Mixed-Race	1 (2)	55 (100)	56 (50)
Age at enrollment – median [IQR]	27.4 [21.9; 31.6]	24.0 [21.7; 27.5]	24.9 [21.7; 30.6]
Married/cohabiting	19 (34)	23 (42)	42 (38)
Educational achievement			
Primary education	6 (11)	2 (4)	8 (7)
Some secondary education	35 (63)	34 (62)	69 (62)
Completed secondary education	11 (20)	18 (33)	29 (26)
Tertiary education	4 (7)	1 (2)	5 (5)
Employed	6 (11)	12 (22)	18 (16)
Average household income			
< R1000/month	31 (55)	28 (51)	59 (53)
R1000 - R5000/month	22 (39)	17 (31)	39 (35)
> R5000/month	3 (5)	10 (18)	13 (12)
SES quartile			
Lowest SES	28 (50)	15 (27)	43 (39)
Low-moderate SES	11 (20)	18 (33)	29 (26)
Moderate-high SES	12 (21)	9 (16)	21 (19)
Highest SES	5 (9)	13 (24)	18 (16)
Primigravid	14 (25)	21 (38)	35 (32)
HIV-infected	21 (38)	0 (0)	21 (19)
Median recent life events experienced [IQR]	1 [0; 1.5]	2 [1; 5]	1 [0; 3]
Lifetime tobacco use	7 (13)	38 (69)	45 (41)
Antenatal tobacco use	2 (4)	31 (56)	33 (30)
Lifetime alcohol use	8 (14)	38 (69)	46 (41)
Antenatal alcohol use	2 (4)	7 (13)	9 (8)
Antenatal depression (BDI-II) – above threshold	16 (29)	16 (29)	32 (29)
Antenatal depression (EPDS) – above threshold	15 (27)	14 (25)	29 (26)
Antenatal psychological distress (SRQ) – above threshold	11 (20)	16 (29)	27 (24)
<i>MINI-diagnosed disorders (6 month postpartum study visit)</i>			
Major depressive episode	9 (16)	13 (24)	22 (20)
Alcohol dependence/abuse	5 (9)	9 (16)	14 (13)
TRAUMA EXPOSURE & PTSD			
<i>Self-reported demographic and psychosocial characteristics (antenatal study visit)</i>			
Childhood trauma – above threshold	13 (23)	20 (36)	33 (30)
Any lifetime IPV	21 (38)	34 (62)	55 (50)
Any recent IPV	14 (25)	25 (45)	39 (35)
<i>MINI-diagnosed disorders (6 month postpartum study visit)</i>			
Trauma exposure	41 (73)	39 (71)	80 (72)
PTSD	9 (16)	13 (24)	22 (20)

6.3.4 Infant outcomes

6.3.4.1 Anthropometry

The median (IQR) gestational age at delivery for infants in this study sample was 39 (38, 40) weeks, **Table 6.2**. Fourteen percent of infants were born preterm, 8% had decreased WAZ scores at birth and 15% had reduced HCAZ scores at birth. At age 6 months, the prevalence of decreased WAZ scores in this study sample was 7%, and 2% were found to have reduced HCAZ scores.

Table 6.2 Infant anthropometry at birth and at 6 months of age

Variable ¹	Mbekweni n (%)	TC Newman n (%)	Total n (%)
Number of infants; sets of twins	57 (51); 1	55 (49); 0	112
Gender – Female	34 (60)	24 (44)	58 (52)
Median gestational age at delivery [IQR]	39 [38; 40]	39 [38; 40]	39 [38; 40]
Preterm birth	7 (12)	9 (16)	16 (14)
<i>Infant anthropometry at birth</i>			
Median weight in kg [IQR]	3.1 [2.8; 3.3]	3.0 [2.6; 3.5]	3.0 [2.7; 3.4]
Median WAZ [IQR]	-0.7 [-1.3; 0.1]	-0.9 [-1.5; -0.01]	-0.7 [-1.4; 0.03]
Low WAZ (WAZ of -2 or below)	3 (5)	6 (11)	9 (8)
Median head circumference in cm [IQR]	33 [32; 34]	34 [32; 34]	34 [32; 34]
Median HCAZ [IQR]	-0.6 [-1.4, 0.1]	-0.6 [-1.6, 0.2]	-0.6 [-1.5; 0.1]
Low HCAZ (HCAZ of -2 or below)	7 (12)	10 (18)	17 (15)
<i>Infant anthropometry at 6 months of age</i>			
Median age in months at study visit [IQR], corrected for prematurity at birth	5.9 [5.9; 6.0]	5.9 [5.8; 6.0]	5.9 [5.8; 6.0]
Median weight in kg [IQR]	8.1 [7.1; 8.8]	7.4 [6.5; 8.5]	7.8 [6.7; 8.6]
Median WAZ [IQR]	0.4 [-0.4; 1.4]	-0.1 [-1.0; 0.8]	0.2 [-0.8; 1.0]
Low WAZ (WAZ of -2 or below)	1 (2)	7 (13)	8 (7)
Median change in WAZ between birth and 6 months [IQR]	1.0 [-0.02; 1.9]	0.6 [-0.4; 1.2]	0.8 [-0.2; 1.5]
Median head circumference in cm [IQR]	43 [42; 44.5]	43 [42; 44]	43 [42; 44.3]
Median HCAZ [IQR]	0.2 [-0.6; 1.8]	-0.01 [-0.7; 1.3]	0.2 [-0.6; 1.4]
Low HCAZ (HCAZ of -2 or below)	2 (4)	0 (0)	2 (2)
Median change in HCAZ between birth and 6 months [IQR]	1.3 [-0.04; 2.5]	1.0 [-0.1; 1.8]	1.1 [-0.1; 2.1]

¹ WAZ, Weight-for-age z-score; HCAZ, Head-circumference-for-age z-score

6.3.4.2 Developmental outcomes at age 6 months

The median scaled scores for each site, and for the total study sample fell within the normal range across all Bayley-III subtests (ie. no median scores ≥ 1 SDs below the standardised mean of 10), **Table 6.3**. However, the prevalence of poor infant developmental outcome as demonstrated by dichotomised scaled scores was notable; and ranged from 0.9% (adaptive behaviour (communication)) to 26% (expressive communication and adaptive behaviour (self-direction)). Overall, 69% of infants in the study sample exhibited poor developmental outcomes on at least one of the Bayley-III subtests.

6.3.5 Association between maternal PTSD and infant developmental outcomes at age 6 months

In crude analyses restricted to trauma-exposed mothers ($n = 81$), maternal PTSD was found to be significantly associated with poorer infant developmental outcomes in the fine motor and adaptive behaviour-motor subscales, as measured by a reduction in the median scaled scores. Infants of mothers with PTSD were found to score 1.8 units (95% CI: 0.4; 3.3) lower on average on the fine motor subscale ($p = 0.015$) and 1.5 units (95% CI: 0.5; 2.4) lower on average on the adaptive behaviour (motor) subscale ($p = 0.004$), **Table 6.4**.

While the association between maternal PTSD and poor fine motor outcomes was no longer significant when adjusted for study site and maternal education, maternal PTSD remained significantly associated with poorer outcomes in the adaptive behaviour (motor) subscale when adjusted for study site, alcohol dependence, and infant HCAZ at birth. Infants of mothers with PTSD scored, on average, 1.3 units (95% CI: 2.3, 0.4) lower on the adaptive behaviour-motor subscale compared to infants of mothers without PTSD, independent of study site, alcohol dependence, and infant HCAZ at birth.

Table 6.3 Infant neurodevelopmental outcomes at 6 months of age

Variable	Mbekweni	TC Newman	Total
Number of infants; sets of twins – <i>n</i> (%)	57 (51); 1	55 (49); 0	112
Median age in months at study visit [IQR], corrected for prematurity at birth	6.0 [5.8; 6.2]	5.9 [5.7; 6.3]	6.0 [5.7; 6.2]
Cognitive scale			
Median score [IQR]	11 [8; 12]	10 [8; 11]	10 [8; 12]
Cognitive deficits – <i>n</i> (%)	13 (23)	9 (16)	22 (20)
Language (Communication) scale			
Receptive communication – median score [IQR]	10 [9; 12]	11 [8; 12]	11 [8; 12]
Receptive communication deficits – <i>n</i> (%)	13 (23)	12 (22)	25 (22)
Expressive communication – median score [IQR]	11 [9; 14]	10 [7; 13]	11 [7; 13.5]
Expressive communication deficits – <i>n</i> (%)	13 (23)	16 (29)	29 (26)
Motor scale			
Fine motor – median score [IQR]	13 [12; 15]	13 [11; 15]	13 [12; 15]
Fine motor deficits – <i>n</i> (%)	2 (4)	3 (5)	5 (4)
Gross motor – median score [IQR]	11 [9; 12]	11 [8; 13]	11 [8; 12]
Gross motor deficits – <i>n</i> (%)	4 (7)	8 (15)	12 (11)
Social-emotional scale			
Median score (IQR)	13 [11; 15]	14 [11; 16]	13 [11; 15]
Social-emotional deficits – <i>n</i> (%)	1 (2)	7 (13)	8 (7)
Adaptive behavior scale			
Communication – median score [IQR]	11 [9; 12]	11 [10; 12]	11 [10; 12]
Communication deficits – <i>n</i> (%)	0 (0)	1 (2)	1 (0.9)
Health and safety – median score [IQR]	10 [9; 10]	10 [10; 10]	10 [9; 10]
Health and safety deficits – <i>n</i> (%)	3 (5)	1 (2)	4 (4)
Leisure – median score [IQR]	10 [9; 12]	11 [10; 13]	11 [9; 12]
Leisure deficits – <i>n</i> (%)	4 (7)	6 (11)	10 (9)
Self-care – median score [IQR]	10 [9; 12]	11 [10; 12]	11 [10; 12]
Self-care deficits – <i>n</i> (%)	4 (7)	3 (5)	7 (6)
Self-direction – median score [IQR]	10 [7; 11]	10 [7; 12]	10 [7; 11]
Self-direction deficits – <i>n</i> (%)	15 (26)	14 (25)	29 (26)
Social – median score [IQR]	11 [11; 12]	12 [11; 13]	12 [11; 13]
Social deficits – <i>n</i> (%)	2 (4)	0 (0)	2 (2)
Motor – median score [IQR]	11 [10; 12]	11 [10; 12]	11 [10; 12]
Motor deficits – <i>n</i> (%)	5 (9)	7 (13)	12 (11)
Any deficits across all scales – <i>n</i> (%)	40 (70)	37 (67)	77 (69)

Table 6.4 Adjusted associations between maternal PTSD and (A) infant fine motor outcomes and (B) infant adaptive behavior (motor) outcomes at 6 months of age, restricted to trauma-exposed mothers (*n* = 81)

Variable	(A) Adjusted associations between maternal PTSD and infant fine motor outcomes				(B) Adjusted associations between maternal PTSD and infant adaptive behaviour - motor outcomes			
	Crude regression coefficient [95% CI]	<i>P</i> -value	Adjusted regression coefficient [95% CI]	<i>P</i> -value	Crude regression coefficient [95% CI]	<i>P</i> -value	Adjusted regression coefficient [95% CI]	<i>P</i> -value
Recruitment site								
Mbekweni	Reference		Reference		Reference		Reference	
TC Newman	-0.3 [-1.6; 1.1]	0.684	-0.1 [-1.5; 1.2]	0.848	0.01 [-0.9; 0.9]	0.990	0.2 [-0.6; 1.1]	0.599
Maternal educational achievement								
Tertiary education	Reference		Reference		Reference			
Completed secondary education	-2.9 [-6.6; 0.]	0.119	-2.3 [-6.1; 1.4]	0.216	-1.0 [-3.5; 1.6]	0.460		
Some secondary education	-2.2 [-5.7; 1.3]	0.222	-1.8 [-5.3; 1.8]	0.327	-1.0 [-3.4; 1.5]	0.437		
Primary education	-5.7 [-10.5; -0.8]	0.023	-4.7 [-9.6; 0.2]	0.061	-1.0 [-4.4; 2.4]	0.558		
Lifetime IPV								
Below threshold	Reference				Reference			
Above threshold	0.1 [-1.3; 1.4]	0.936			-1.1 [-2.0; -0.3]	0.012		
Recent IPV (antenatal)								
Below threshold	Reference		Reference		Reference			
Above threshold	-1.0 [-2.5; 0.4]	0.152	-1.0 [-2.5; 0.4]	0.152	-1.7 [-2.6; -0.8]	< 0.001		
Antenatal alcohol use								
No self-reported alcohol use	Reference				Reference			
Self-reported alcohol use	-1.2 [-3.7; 1.4]	0.371			-2.1 [-3.7; -0.4]	0.017		
MINI-diagnosed alcohol dependence/abuse								
No alcohol dependence/abuse	Reference				Reference		Reference	
Alcohol dependence/abuse	-0.3 [-2.3; 1.7]	0.775			-1.4 [-2.7; -0.1]	0.036	-1.3 [-2.5; -0.1]	0.035
Infant WAZ at birth	0.5 [-0.2; 1.1]	0.152			0.5 [0.03; 0.9]	0.038		
Infant WAZ at 6 months	-0.1 [-0.6; 0.4]	0.719			0.2 [-0.2; 0.5]	0.401		
Change in infant WAZ: birth – 6 months	-0.4 [-0.9; 0.1]	0.153			-0.1 [-0.5; 0.2]	0.449		
Infant HCAZ at birth	0.3 [-0.3; 1.0]	0.295			0.5 [0.1; 0.9]	0.010	0.4 [0.03; 0.8]	0.033
Infant HCAZ at 6 months	0.3 [-0.2; 0.8]	0.217			0.2 [-0.1; 0.5]	0.285		
Change in infant HCAZ: birth – 6 months	0.1 [-0.4; 0.5]	0.692			-0.1 [-0.4; 0.2]	0.407		
PTSD diagnosis								
No PTSD	Reference		Reference		Reference		Reference	
Lifetime/current PTSD	-1.8 [-3.3; -0.4]	0.015	-1.5 [-3.0; 0.1]	0.060	-1.5 [-2.4; -0.5]	0.004	-1.3 [-2.3; -0.4]	0.007

6.4 Discussion and conclusions

In this study of mother-infant data from the DCHS, maternal PTSD was found to be significantly associated with poorer infant developmental outcomes in the fine motor and adaptive behaviour (motor) subscales (crude analyses); the latter association remained significant when adjusted for study site, alcohol dependence, and infant HCAZ at birth.

While one small-scale study recently reported that exposure to maternal PTSD may be associated with emotion regulation difficulties in infancy (Enlow et al. 2011), to the best of our knowledge ours is the first to investigate specifically the association between maternal PTSD and infant neurodevelopment in a LMIC setting. However, our findings are consistent with a growing body of work on the detrimental effect of maternal anxiety on infant and child neurodevelopment. For example, in their prospective study of 170 mother-infant dyads, Huizink and colleagues (2003) reported that higher levels of maternal pregnancy-specific anxiety predicted lower mental and motor developmental scores at infant age 6 months. Similarly, in their investigation of 105 Caucasian mother-infant dyads, Brouwers and colleagues (2001) found that high maternal anxiety during late pregnancy was associated with lower mental developmental scores on the Bayley Scales of Infant Development at age 2 years. More recently, Hadley and colleagues (2008) have reported that maternal symptoms of common mental disorders (including anxiety and depression) were significantly associated with poorer motor, language and social development of 431 infants aged 3 to 24 months in a rural Ethiopian setting.

It is interesting to note that maternal PTSD was associated only with deficits in fine motor infant development in this study sample. More specifically, a statistically significant effect on cognitive or language neurodevelopment was not demonstrated. This is seemingly inconsistent with prior work in this field. For example, in their prospective investigation of 58 mother-infant dyads exposed to a natural disaster during pregnancy (an ice storm in Québec, Canada – January 1998), Laplante and colleagues (2004) reported that high levels of prenatal stress were associated both with lower general intellectual performance (on the Bayley Mental Development Index (MDI)), and poorer receptive language abilities. As discussed in Chapters 3

(Section 3.4 – Discussion and conclusions, p 39) and 5 (Section 5.4 – Discussion and conclusions, p 97-98), this inconsistency may be due to our relatively small sample size with limited power to detect effects of smaller sizes; or to developmental testing at an age too early to detect subtle associations.

Several different mechanisms for such an association between maternal stress and anxiety and deficits in infant neurodevelopment have been proposed, including hyperactivity of the HPA-axis, with resultant hypercortisolism in both the mother and the infant (Glover et al. 2010; Talge et al. 2007; Van den Bergh et al. 2005). Epigenetic modifications via glucocorticoid receptor methylation (“silencing”) in children exposed to maternal trauma, stress and anxiety (Radtke et al. 2011; Stein et al. 2014) as well as behavioural components associated with maternal PTSD such as hypervigilance or readily distracted attention (Talge et al. 2007) also may contribute to impaired infant neurodevelopment.

A number of key limitations should be borne in mind when considering our study findings. First, our study sample was relatively small, thus reducing the power to detect potentially significant associations such as those between maternal exposure to psychological trauma and infant developmental outcomes. Second, data on certain psychosocial risk factors (including psychological distress and alcohol or tobacco use) were obtained from self-report assessment tools, which may have biased these findings. Third, all MINI data included in these analyses were taken from the 6-month (postnatal) timepoint, which is concordant with the timing of the infant developmental assessments. However, given that posttraumatic symptomatology must be present for at least 1 month to meet the DSM-IV diagnostic criteria for PTSD (APA 2013), it is not unreasonable to assume that – at least a proportion of – the maternal PTSD cases preceded the onset of poor infant developmental outcomes. Fourth, potential moderators and mediators in the relationship between maternal PTSD and infant neurodevelopment (such as partner support and parenting style) were not included in this analysis. Fifth, while it is possible that unmeasured confounders influenced our findings, we attempted to minimise residual confounding by adjusting for key variables such as study site and SES. Finally, the large number of bivariate analyses (in which the outcome of interest was scaled scores on each subtest of the

Bayley III assessment) may have introduced Type I error. That said, these analyses were intended to be exploratory in nature, with the final multiple regression model informing the key findings in this study.

Despite these limitations, the prospective nature of our study has made possible one of the first tests of the association between maternal PTSD and subsequent deficits in infant neurodevelopment, and the first in a LMIC context. However, our findings should nonetheless be taken as preliminary, given the number of tests completed and the limited power to control for the full range of possible moderators, mediators and confounders. A focus on infant and child development is particularly relevant in LMIC settings. Two recent reviews of data from developing countries (Grantham-McGregor et al. 2007; Walker et al. 2007, 2011; Engle et al. 2007, 2011; Lake 2011) emphasised that more than 200 million children under the age of 5 years do not reach their cognitive developmental potential in this context. Given the high prevalence of exposure to trauma and PTSD in pregnant women, our preliminary data may be important for informing culturally-appropriate health promotion, screening and intervention campaigns.

The next chapter – based on the fifth, and final, publication – will explore the genetic risk factors associated with the development of PTSD among traumatised individuals in this cohort, thereby addressing the final research objective of this thesis.

CHAPTER 7

PUBLICATION 5

Association between *RGS2* and posttraumatic stress disorder in the Drakenstein Child Health Study

Authors

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Synopsis

As the final manuscript included in this thesis, this is the first to include aspects of genetic analyses, and thus will address specifically the fifth and final research objective (*see Chapter 1, Section 1.6 – Study objectives and related publications, p 7*):

To determine the association between variants in specific candidate genes (which previously have been identified as being associated with the stress response and PTSD) and PTSD in this cohort.

Written in collaboration with co-authors and colleagues at Emory University, Atlanta, GA, USA, this manuscript is in submission to *Acta Neuropsychiatrica* (the official Journal of Scandinavian College of Neuropsychopharmacology), an international journal with a focus on translational neuropsychiatry.

Abstract

Introduction

Studies of PTSD provide heritability estimates ranging from 30% to 46%, and specific genetic variants may confer increased risk for PTSD in traumatised individuals. Despite the growing body of work, there remains a paucity of data from populations of African ancestry. We investigated the association between PTSD candidate genes and the development of this disorder among traumatised women in the DCHS, in which mothers have been found to have a high prevalence of trauma and PTSD.

Methods

Sociodemographic characteristics and data on PTSD symptomatology were collected using self-report and clinician-administered tools. Genotyping was done using the PsychArray BeadChip from blood DNA. Logistic regression analyses were used to determine the association between

33 selected candidate genes and PTSD, using principal component as a covariate to correct for population stratification.

Results

Data from 374 mothers were included. The vast majority (89%) reported exposure to at least one traumatic event in their lifetimes; with almost a third above threshold for PTSD. Among the 33 selected single nucleotide polymorphisms (SNPs), one SNP in the 3'-untranslated region (3'-UTR) of the regulator of the G-protein signaling 2 (*RGS2*) gene, rs4606, was found to be significantly associated with lifetime PTSD in this cohort, after correction for multiple testing.

Conclusion

This study represents the first data of an association between a SNP in the *RGS2* gene and PTSD in a population of African ancestry. This finding is consistent with prior work on anxiety in animals and humans; and with one study of PTSD in European-Americans. Further work in unique and under-studied populations such as ours would be useful to delineate the role of *RGS2* and related variants in the development of PTSD.

Keywords: PTSD, females, genetics, *RGS2*, South Africa

7.1 Introduction

To date, studies of PTSD have provided heritability estimates ranging from 30% to 46% (Skelton et al. 2012; Sartor et al. 2011, 2012; Brewin et al. 2000; True et al. 1993; Koenen et al. 2008a). These include family studies, reporting that relatives of individuals with the disorder are at higher risk of PTSD than control relatives (Koenen et al. 2008b; Sack et al. 1995; Yehuda et al. 2001a); and twin studies, which aim to delineate genetic and environmental risk factors for this disorder (True et al. 1993; Stein et al. 2002). More recently, focused candidate gene studies have identified a number of stress-related polymorphisms which may confer increased vulnerability to PTSD. These include variants in the monoamine (Kilpatrick et al. 2007; Kolassa et al. 2010a,b; Segman et al. 2002; Comings et al. 1996; Voisey et al. 2009), neurotrophic (Zhang et al. 2014; Hemmings et al. 2013), peptidergic (Ressler et al. 2011); and HPA-axis-related systems (Binder et al. 2008; White et al. 2013; Boscarino et al. 2012), all of which have been shown to play a role in the stress response in animals and in the neurobiology of PTSD in humans.

Despite the growing body of work on the genetics of PTSD, there is a paucity of data from populations of African ancestry such as those in South Africa. According to nationally representative studies, most South Africans experience some traumatic event in their lifetimes (Williams et al. 2007). Prior work by our group in the DCHS has found that approximately a third of participants in this setting are above threshold for PTSD (*see Chapter 4 – Publication 2, p 55-56; Koen et al. 2014*). South Africa has unique ethnolinguistic populations, some with ancient genomes and great variability (Tishkoff & Williams 2002). These populations are particularly heterogeneous, owing to historical patterns of migration and relocation, and are thus particularly informative for novel studies of complex genetic diseases (Tishkoff & Williams 2002). Thus, South Africa and similar LMIC countries provide a unique opportunity for the study of PTSD and other trauma- and stressor-related disorders. This study will aim to address the gap in current scientific and clinical knowledge; and the association between specific candidate genes and the development of PTSD among traumatised women in a South African birth cohort study.

7.2 Methods

This study reports data from the DCHS. Details of participant enrollment can be found in *Chapter 2, Section 2.3 – Participant recruitment and follow-up (p 9-10)*; and ethical processes relevant to this study in *Chapter 2, Section 2.5 – Ethical considerations (p 20-21)*.

7.2.1 Phenotype assessment

As described in *Chapter 2, Section 2.4 – Measures and variable calculation (p 10-18)*, enrolled women were assessed at 28 – 32 weeks' gestation using self-report and clinician-administered measures, as follows:

- a) **Sociodemographic characteristics** – SES was assessed using a questionnaire designed for the DCHS.
- b) **Trauma exposure and PTSD** – the Modified PTSD Symptom Scale (MPSS) (Foa et al. 1993) and the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al. 1997; Sheehan et al. 1997, 1998) were used to assess lifetime PTSD from a number of antenatal and postnatal timepoints. Based on their responses to the MPSS and MINI items, participants were categorised into three groups – those having no trauma exposure; those with trauma exposure but no PTSD; and those who developed PTSD following trauma exposure.

Those women with suspected PTSD (or other psychopathology) on the self-report or clinician-administered measures were referred to local health service providers according to a standard operating procedure designed for this study. Educational pamphlets produced by the study team were distributed to all study participants, to facilitate self-directed healthcare seeking.

7.2.2 Statistical analyses

All data were analysed using *Stata 12* (StataCorp Inc, College Station, Texas, USA). Frequency distributions and medians (interquartile ranges) were used to describe sociodemographic variables (age, marital status, educational attainment, income); trauma exposure; and PTSD. In order to maximise the number of participants in our analyses, PTSD diagnosis based on the MPSS and MINI were combined to provide information on lifetime PTSD. Participants were categorised as either having no trauma exposure; or trauma-exposed but no lifetime PTSD; or having lifetime PTSD. In our genetic analyses, we included only participants with trauma exposure but without lifetime PTSD (as controls); and participants with lifetime PTSD (as cases).

7.2.3 Genetic analyses

Blood samples were collected on-site from participants at enrollment by trained study nurses, and samples transported to dedicated laboratory facilities at Red Cross Children's Hospital, Cape Town, South Africa. DNA was extracted from blood samples using the QIAasymphony® DSP DNA Midi kit and protocol. DNA was quantified using BioDrop (Whitehead Scientific, South Africa) and normalised to a concentration of 5-10ng/ul. All samples were tracked using a Laboratory Information Management System (LIMS; Freezerworks, USA).

Genotyping was performed at Emory University, Atlanta, GA, USA. Genome-wide SNP genotyping was conducted using the Illumina Infinium PsychArray Beadchip, a GWAS-based Illumina custom array containing about 271,406 Tag single nucleotide polymorphisms (SNPs) and approximately 50,000 markers associated with common psychiatric disorders. This is a cost-effective, high-density micro-array designed for large-scale genetic studies focused on psychiatric predisposition and risk. The combination of rare psychiatric-relevant markers, Tag SNPs, and exome content make the PsychChip the ideal array for our setting. We selected for analysis 33 candidate SNPs which have been identified as associated with the stress response and PTSD in prior work (Nievergelt et al. 2015; Rothbaum et al. 2014). Genome-wide genotype data were used by the Psychiatric Genomics Consortium (PGC) to impute all 33 candidate SNPs

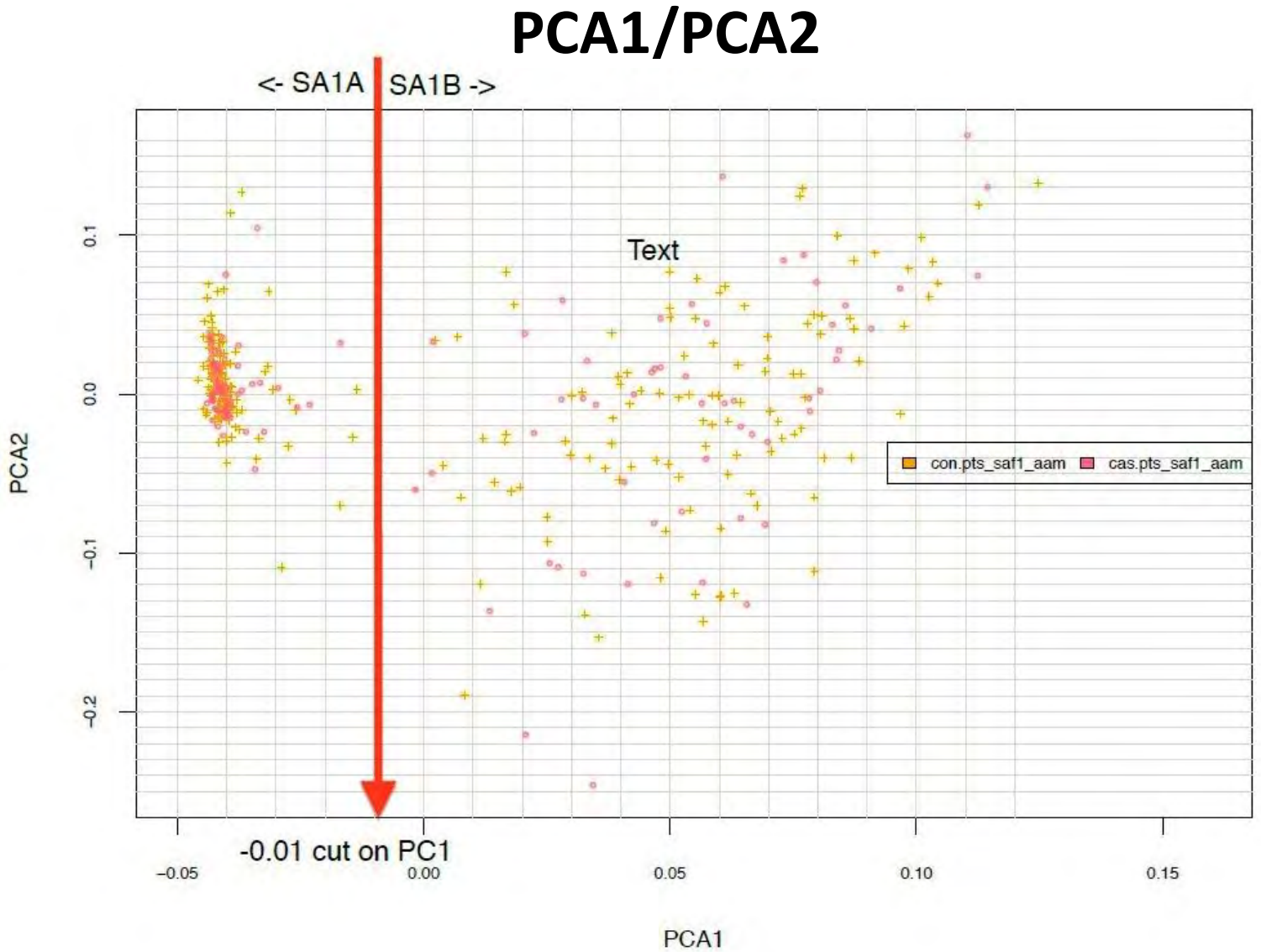
used in the analyses; genome-wide association data were also used to calculate the Principal Component (PC) to correct for population stratification (see below).

Standard quality control of the genome-wide data was performed by the PGC, first removing SNPs with call rates < 95%, and individuals with greater than 2% missing data; then removing SNPs with call rates < 98%, those with a missing difference between case and control greater than 0.020, and those with Hardy-Weinberg equilibrium (HWE) p -values < 1×10^{-6} in controls and < 1×10^{-10} in PTSD patients. We also removed one in each pair of related individuals with an identity by descent proportion > 0.12 (indicating cousins or a closer relation). PC eigenvectors of the genetic relationship matrix were calculated using independent autosomal SNPs with an r^2 of 0.05 for non-imputed SNPs (following the quality control procedures as described above). Statistical analysis showed that PC1 was sufficient to account for population sub-structure.

The study population was divided by the PGC into two subgroups based on ancestry: one including women of only African Ancestry ($n = 218$) (Subpopulation A), and one including women of Mixed Ancestry ($n = 157$) (Subpopulation B); outliers were excluded from the analyses (**Figure 7.1**). The association between the selected SNPs and PTSD diagnosis was examined in each subgroup using logistic regression, in which PTSD status was the outcome, SNP genotype the independent continuous variable, and the first principal component as the covariate. We used the additive model for the genotype, with the minor allele coded as 1. Multiple testing was addressed with Bonferroni correction. Results from each subpopulation were then meta-analysed.

Figure 7.1 Principal component plots

- A.** The first two principal components (PCA1 and PCA2) were able to be separated into Subpopulation A (African Ancestry only) and Subpopulation B (Mixed Ancestry):
- Subpopulation A (SAFRA) $PCA1 < -0.01$
 - Subpopulation B (SAFRB) $PCA1 > -0.01$ (*indicated by the vertical line*)

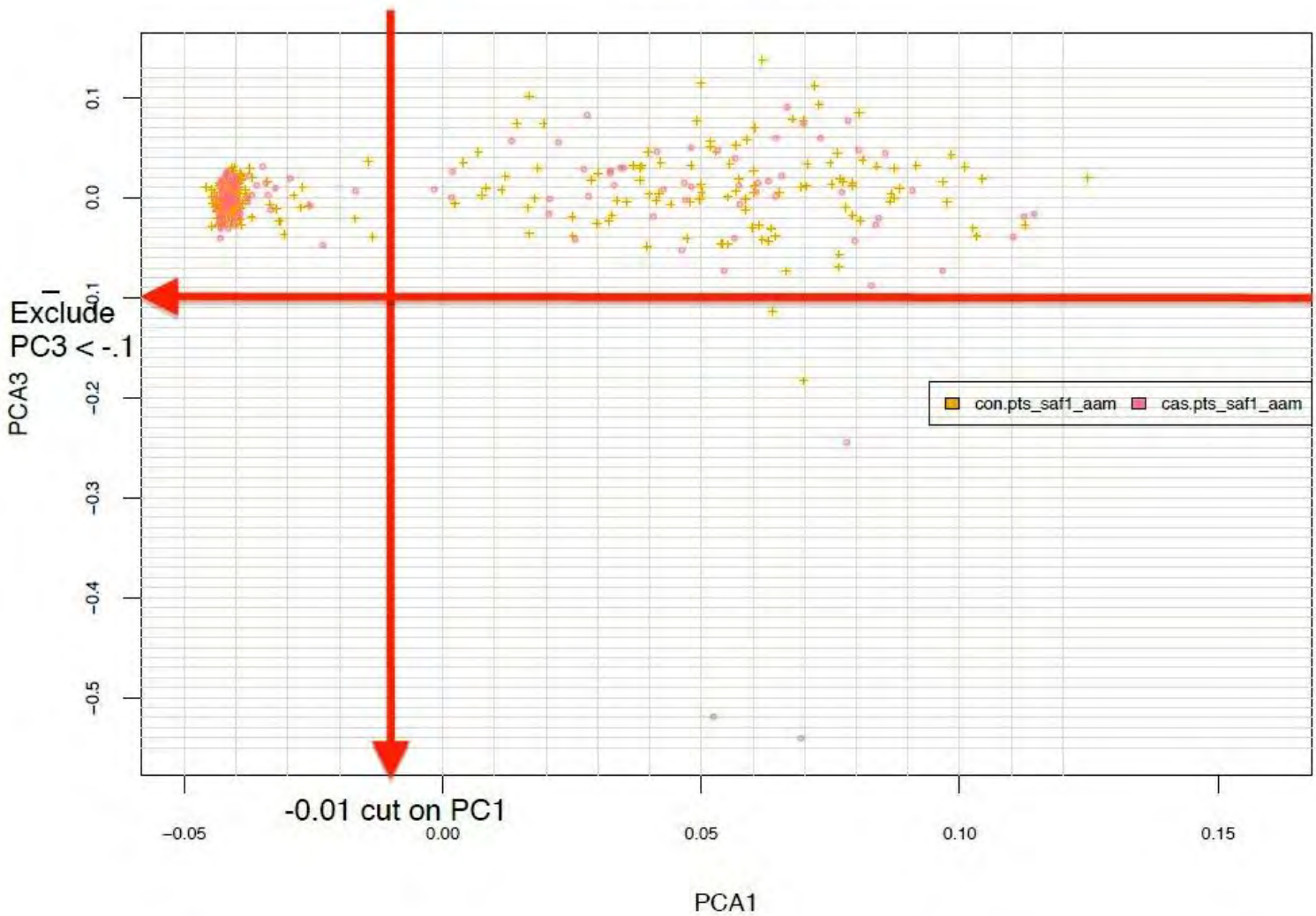


B. PCA1 and PCA3 were able to distinguish Subpopulations A and B; and to exclude a few outliers:

- SAFRA PCA1 < -0.01 and PCA3 > -0.01
- SAFRB PCA1 > -0.01 and PCA3 > -0.01

Samples with PCA3 < -0.01 were considered outliers and excluded from the analyses (5 samples).

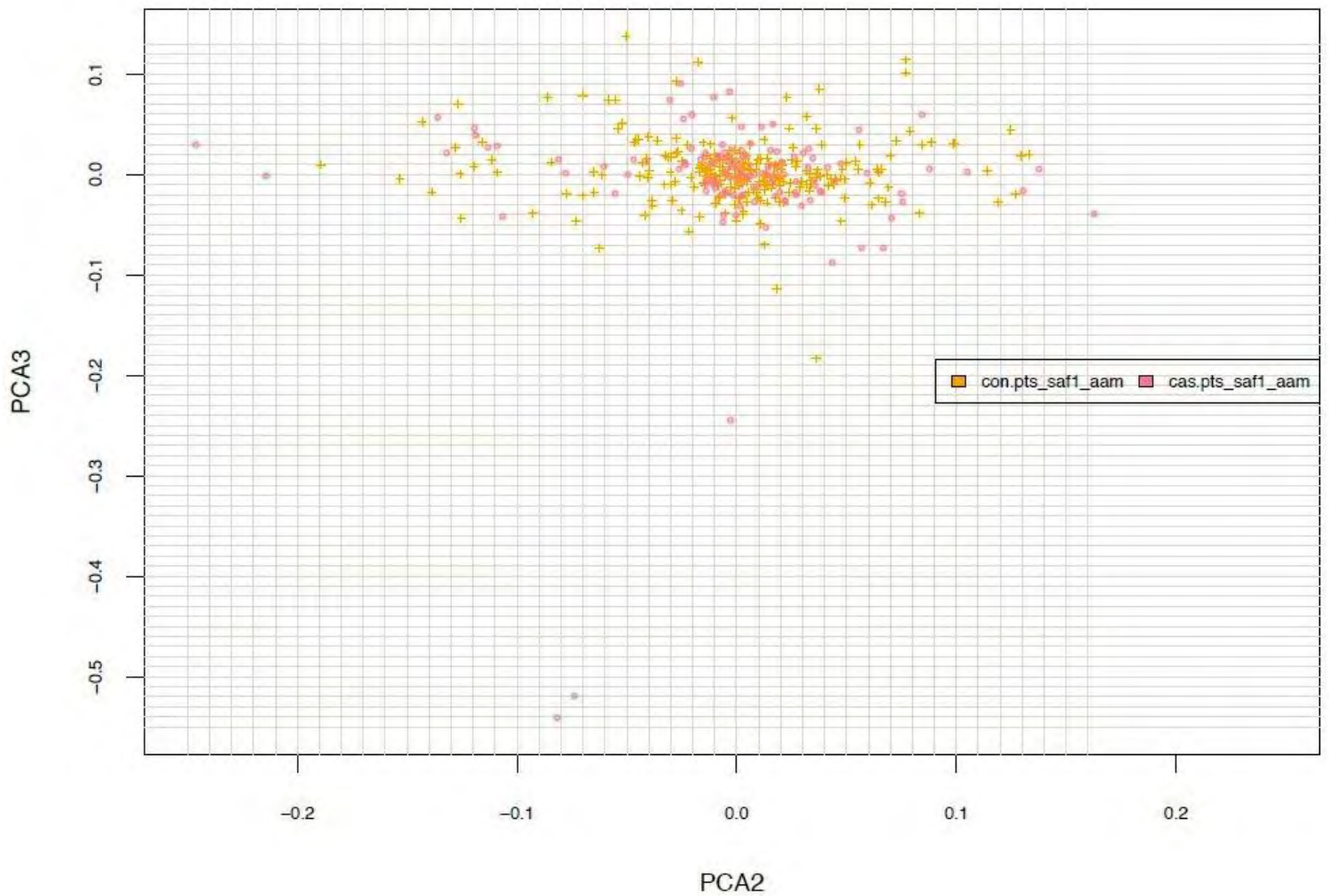
PCA1/PCA3



C-F) Principal component plots: PCA2/PCA3, PCA2/PCA4, PCA3/PCA4, PCA5/PCA6; these components were not able to distinguish SAFRA from SAFRB but were able to identify a few more outliers to be excluded.

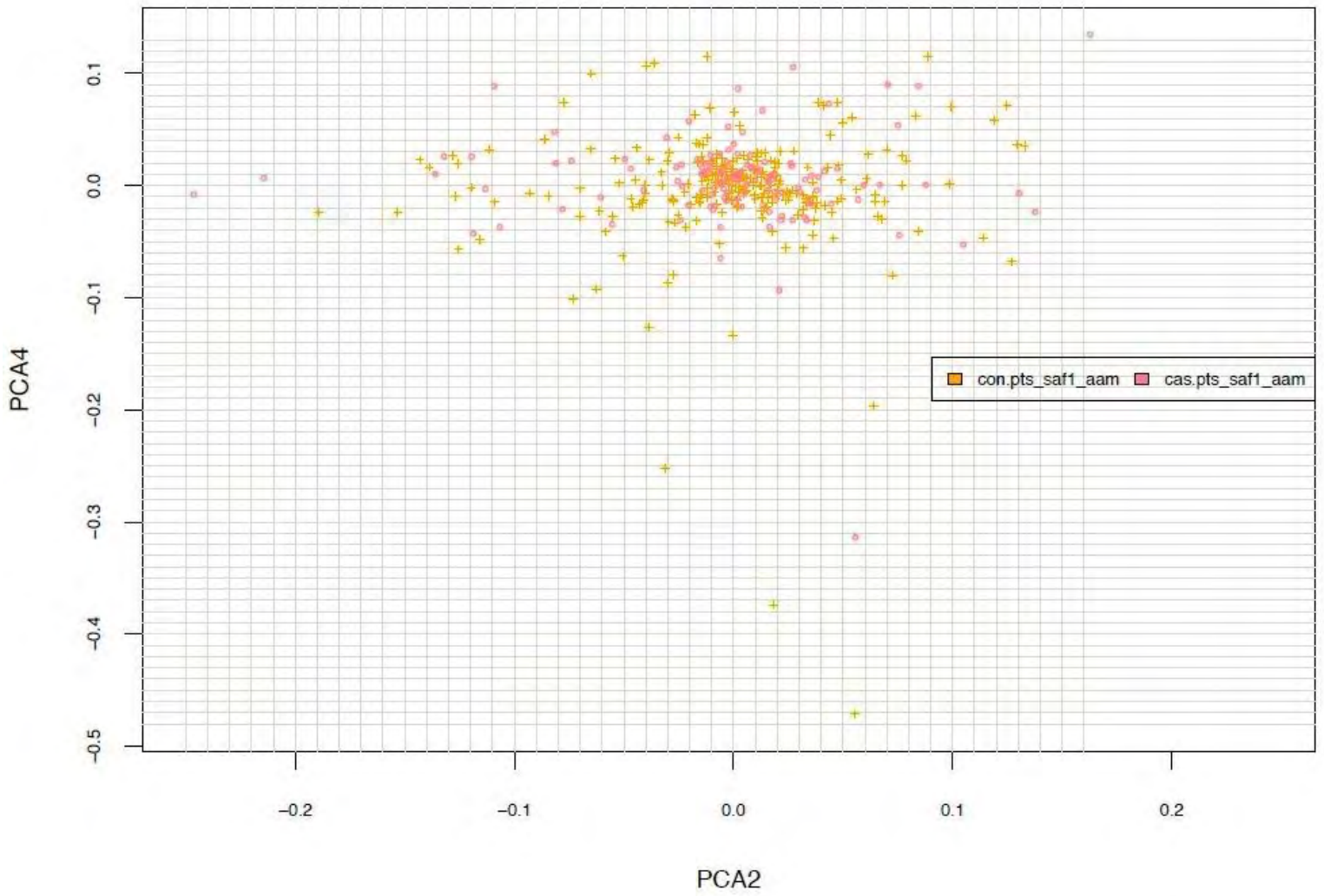
C. PCA2 and PCA3 plot

PCA2/PCA3



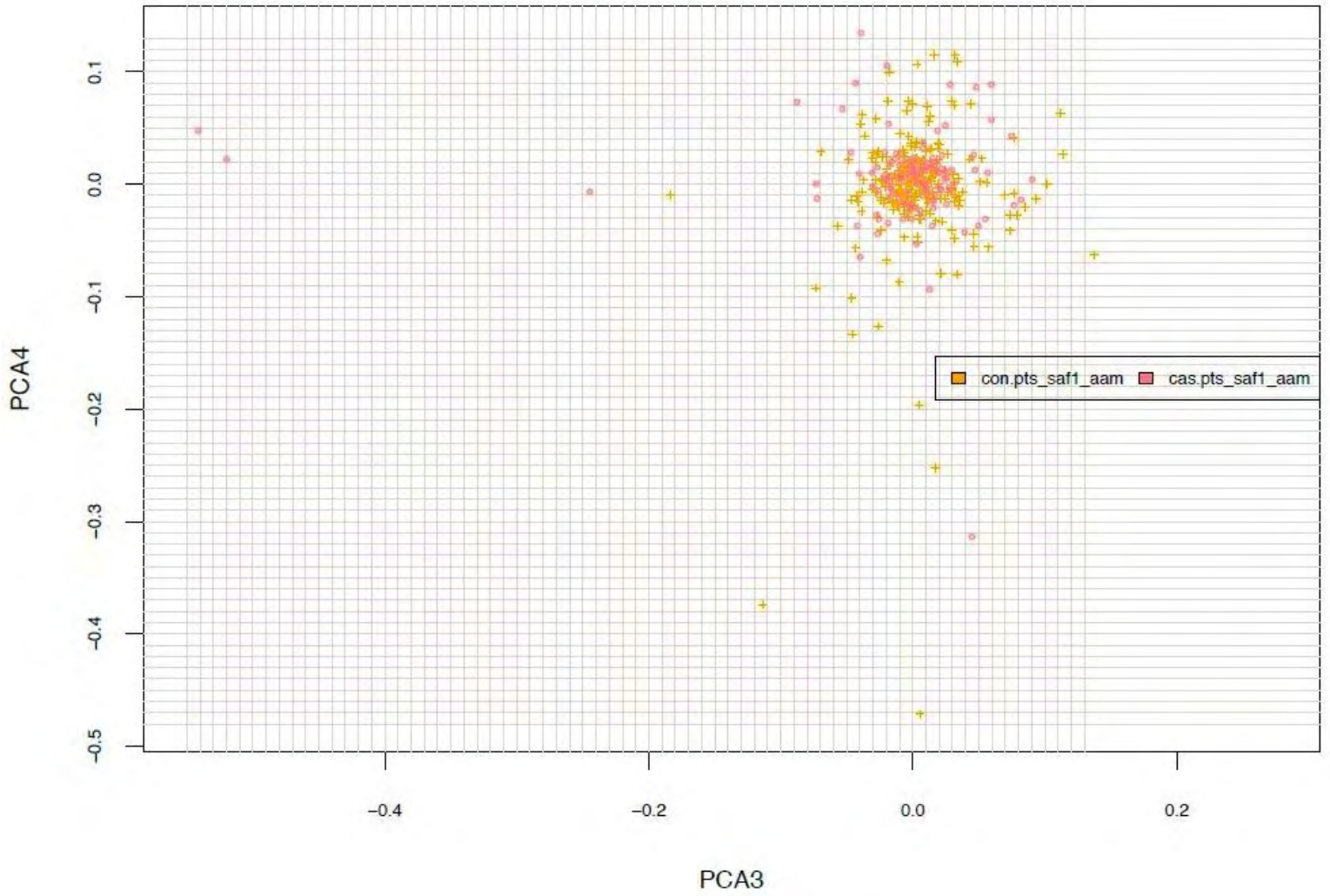
D. PCA2 and PCA4 plot

PCA2/PCA4



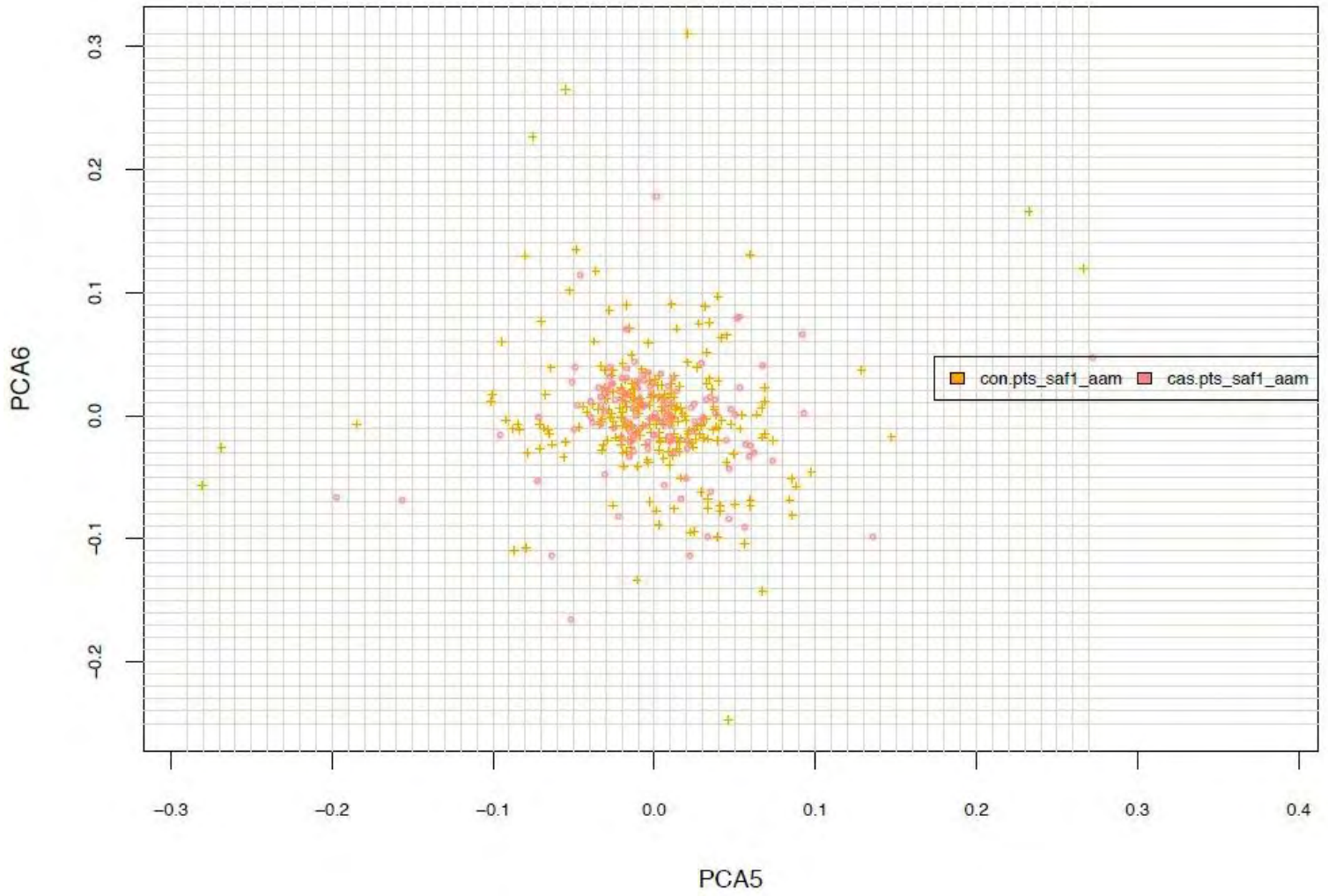
E. PCA3 and PCA4 plot

PCA3/PCA4



F. PCA5 and PCA6 plot

PCA5/PCA6



7.3 Results

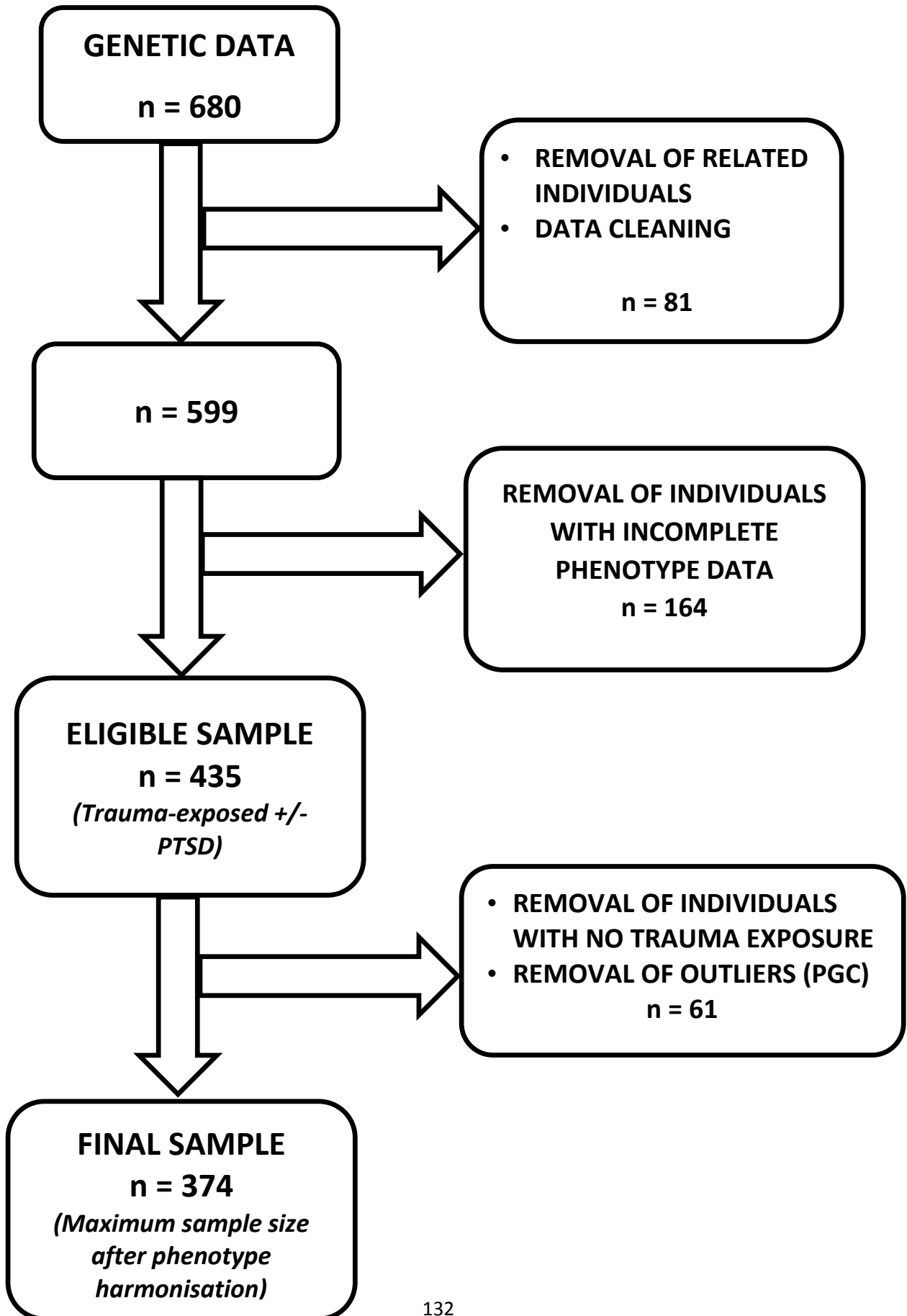
7.3.1 Maternal sociodemographic characteristics

DNA from 680 enrolled mothers was collected between March 2012 and May 2014. After data cleaning and removal of related individuals, 599 samples were available for analyses. Within this population, 435 participants were eligible for this study as they were categorised as being trauma-exposed (but with no PTSD), or as being above threshold for PTSD on either the MPSS or the MINI (after data harmonisation). During the process of imputing all missing SNPs, outliers were removed by the PGC. Thus, the final analysis comprised data from 374 mothers, divided by ancestry, **Figure 7.2**. The median age of study participants at enrollment was 22 years, **Table 7.1**. The vast majority (78%) was unemployed; and the average household income was \leq R5,000 in most cases (85% of the study sample).

Table 7.1 Maternal sociodemographic characteristics, trauma exposure and phenotype data

Variable	Mbekweni n (%)	TC Newman (%)	Total n (%)
Number of mothers	212 (57)	162 (43)	374
Baseline demographic characteristics (n = 374)			
Ethnicity			
Black/African	211 (99.5)	2 (1)	213 (57)
Mixed Ancestry	1 (0.5)	160 (99)	161 (43)
Age at enrollment – median [IQR]	22.2 [26.6; 31.4]	21.3 [24.9; 29.4]	22.0 [25.9; 30.7]
Employed	41 (19)	41 (25)	82 (22)
Average household income			
< R1000/month	105 (50)	55 (34)	160 (43)
R1000 - R5000/month	79 (37)	79 (49)	158 (42)
> R5000/month	28 (13)	28 (17)	56 (15)
SES quartile			
Lowest SES	85 (40)	37 (23)	122 (33)
Low-moderate SES	54 (25)	40 (25)	94 (25)
Moderate-high SES	49 (23)	46 (28)	95 (25)
Highest SES	24 (11)	39 (24)	63 (17)
Trauma exposure & phenotype data			
MINI phenotype (n = 313)			
No exposure	22 (13)	12 (9)	34 (11)
Trauma-exposed (no PTSD)	108 (63)	86 (61)	194 (62)
PTSD	42 (24)	43 (31)	85 (27)
MPSS phenotype (n = 338)			
No exposure	67 (35)	74 (51)	141 (42)
Trauma-exposed (no PTSD)	58 (30)	42 (29)	100 (30)
PTSD	67 (35)	30 (21)	97 (29)

Figure 7.2 Study flow figure of sample selection



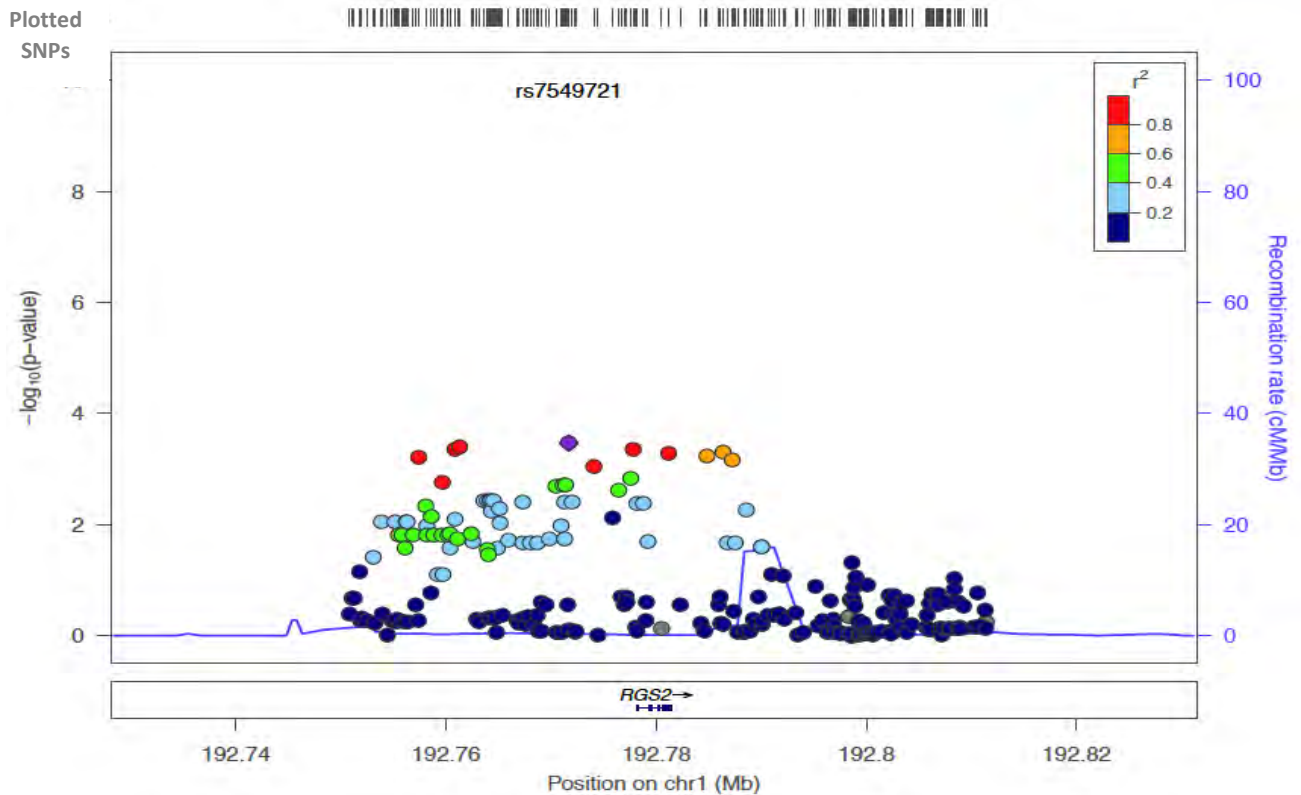
7.3.2 Trauma exposure and PTSD

Most participants (89%) reported exposure to at least one traumatic event in their lifetimes during MINI assessment, **Table 7.1**. In this study sample, almost a third of participants developed PTSD, as assessed by the self-report MPSS (yielding a PTSD prevalence of 27%), and the clinician-administered MINI (PTSD prevalence of 29%).

7.3.3 Genetic polymorphisms conferring increased risk for PTSD

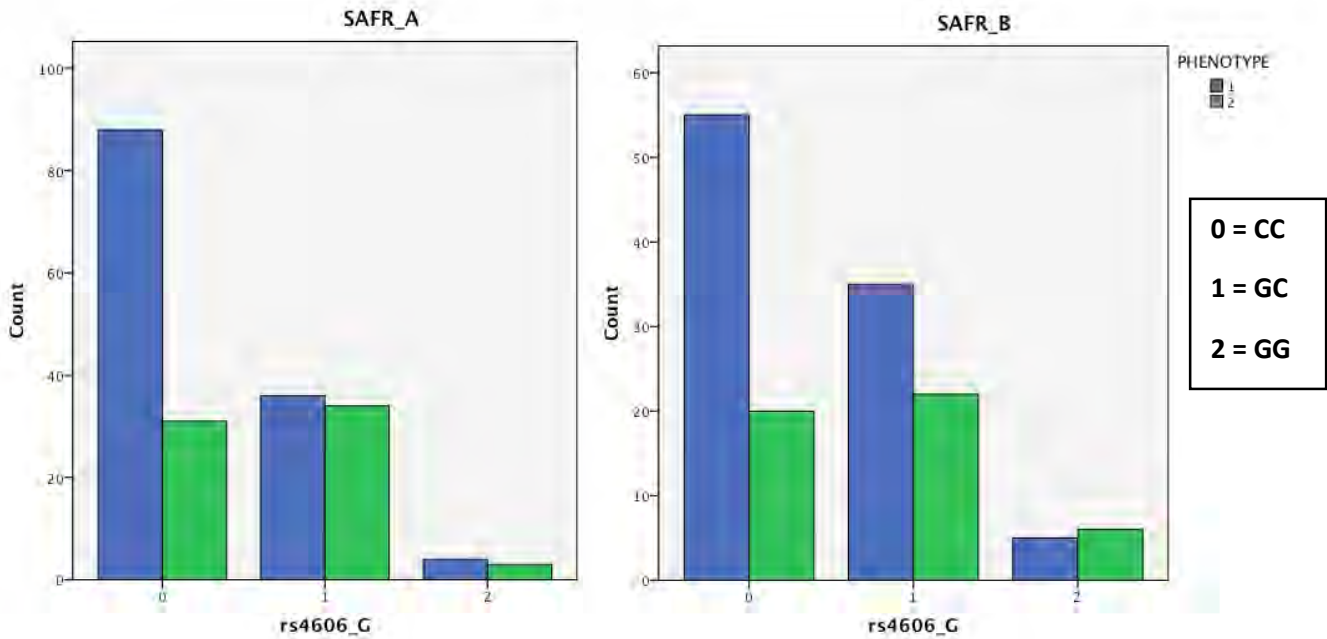
After performing meta-analyses of the results from the two independent subpopulations (A and B), one SNP – rs4606 – located within exon 5 of the Regulator of G-protein Signaling 2 (*RGS2*) gene, survived Bonferroni correction ($0.05/32 = 0.0015625$) ($p = 0.000521$). This SNP was found to have the lowest p -value in Subpopulation A ($p = 0.001976$), and the second lowest ($p = 0.0748$) in Subpopulation B. The regional *RGS2* gene locus of the meta-analysed p -values showed a cloud of SNPs in the *RGS2* within one recombination block, with all reaching p -values in the order of $10e-3$, **Figure 7.3**. Almost all SNPs were located in the 5' site of the gene, implicating a possible regulatory function of the candidate SNPs. The G allele (minor allele) was associated with PTSD in both subpopulations, but particularly Subpopulation A, **Figure 7.4**.

Figure 7.3 Regional *RGS2* locus association plot



Allelic variation in the *RGS2* locus is shown in the association plot with PTSD diagnosis. The X-axis shows the position of the SNPs and the *RGS2* gene on Chromosome 1 (the gene is represented by the blue line); the arrow indicates the 5'-3' direction. Purple diamonds indicate the SNP with the lowest p -value, which is denoted by the rs number. Circles show all the other mapped SNPs; their colour indicates the strength of linkage disequilibrium (LD) between the top associated SNP and the variant. Red indicates complete LD ($r^2 = 1$); grey indicates no LD ($r^2 = 0$). The Y-axis represents the strength of association as minus log₁₀ of the p -value. The blue line-picks represent the recombination rate in cM/Mb. The meta-analysed p -values show a cloud of SNPs in the *RGS2* within one recombination block (blue) all reaching p values in the order of $10e^{-3}$.

Figure 7.4 Allelic variation in the *RGS2* gene (SNP rs4606)



Allelic variation in the *RGS2* gene (SNP rs4606) was associated with PTSD in both subpopulations (A and B). Figure 7.4 demonstrates PTSD and Control subjects stratified by allelic variants G/C at rs4606 (*RGS2*). The G allele was associated with increased risk of PTSD in both subpopulations ($p = 0.001976$ and $p = 0.0748$ respectively for Subpopulations A and B).

7.4 Discussion and conclusions

To our knowledge, this is the first study to investigate the association between a SNP of the *RGS2* (Regulator of G-protein Signaling 2) gene and PTSD in an African population. In the Drakenstein cohort – a highly traumatised study population with almost a third of participants above threshold for PTSD – we found that rs4606, a polymorphism in the *RGS2* gene, was significantly associated with PTSD, after controlling for population stratification. The G allele (minor allele) was associated with increased risk of developing this disorder in this cohort.

RGS2 is part of a large family of signaling proteins (Hollmann et al. 2005) – the G-protein coupled receptors – which are involved functionally in the activation of intracellular signal transduction and in regulating vasoconstriction (Hollinger & Helper 2002). *RGS2* knock-out has been associated with anxiety in mice (Yalcin et al. 2004); as well as with the development of panic disorder in humans of Asian (Otowa et al. 2011) and European (Leygraf et al. 2006) descent, with the strongest association in the latter study being observed for a haplotype including rs4606 (C as risk allele), a SNP in the 3' UTR of *RGS2*. Variations in rs4606 have been found also to be significantly associated with the development of generalised anxiety disorder in a sample of 607 adults who had been exposed to the 2004 Florida Hurricane (higher prevalence of the C-allele among patients than controls) (Koenen et al. 2009); and with increased vulnerability to suicide (higher prevalence of the G-allele in suicide versus controls) in a Japanese population (Cui et al. 2008). To date, only one study has investigated specifically the association between rs4606 and PTSD (Amstadter et al. 2009). In this gene-environment study of data from the 2004 Florida Hurricanes Study, the rs4606 SNP C-allele (major allele) was found to be associated with increased symptoms of post-hurricane PTSD in the context of low social support and high hurricane exposure. This polymorphism was found also to increase the risk of lifetime PTSD symptoms under the conditions of low social support and lifetime trauma exposure. All interactions remained significant when adjusted for sex, ancestry, and age. As is the case for most work in this field, the vast majority of participants in this study self-reported as European-American. Thus, our study provides a novel complement to these findings, using data from a unique cohort of African and Mixed Ancestry. Further, our focus on female

participants – particularly pregnant women and new mothers – is relevant given that women are more vulnerable to PTSD (Beck et al. 2011; Söderquist et al. 2009; Sartor et al. 2011; Olff et al. 2007). Of interest, it seems that the minor allele (G allele) of the rs4606 SNP confers risk in our cohort, versus the major allele (C allele) in the Florida Hurricanes study (Amstadter et al. 2009). One explanation for this discrepancy may be that rs4606 is not the functional SNP, but rather is in linkage disequilibrium with another SNP.

Given the unique composition of our study sample, it is also notable that no other SNPs previously found to be associated with the stress response and PTSD (see Nievergelt et al. 2015; Rothbaum et al. 2014) were significantly associated with this disorder in the current study. To date, most research has focused on candidate genes in the HPA axis; the noradrenergic (locus coeruleus) system; and the limbic-frontal pathways, particularly those mediating fear processing (Nievergelt et al. 2015; Koenen 2007). For example – and of relevance to our study setting – Hemmings and colleagues (2013) recently reported a significant interaction effect between polymorphisms of the brain-derived neurotrophic factor (BDNF) and dopamine receptor 2 (DRD2) genes on PTSD symptom severity in 150 participants from an at-risk South African population. Our null findings in relation to prior work in this field may be due to a number of factors, including our candidate gene approach – in which the 33 selected SNPs were representative of only a small percentage of the large and diverse genetic risk for PTSD. However, it is also noteworthy that the current body of PTSD candidate gene data remains inconsistent, possibly owing to the notable heterogeneity among the index traumatic events, or to small samples sizes.

The current study has a number of noteworthy limitations. First, we used a candidate gene approach, as our relatively low sample size would not allow for more sophisticated genetic analyses. Second, as genotype imputation was used in this analysis – rs4606 is an imputed SNP – low-frequency variants may not have been captured. Third, recall bias may exist, due to data on trauma exposure and PTSD symptoms being collected over the participants' lifetimes. Finally, our sample size was relatively small, and thus may have diminished our ability to detect potentially significant main effects. Nonetheless, our study may constitute a novel contribution

to the genetic understanding of a complex psychiatric illness in a unique population, the genomic organisation of which is older than many others (Tishkoff & Williams 2002). Despite the adversity faced by many, not all traumatised individuals go on to develop PTSD. Thus, by identifying genetic or other factors that confer increased risk (or resilience) to this disorder, further work in this field may increase the current understanding of the neural circuitry of fear dysregulation; identify genetic pathways contributing to PTSD; and ultimately lead to improved neurobiological knowledge and management of this disorder.

The final chapter of this thesis will contain a general discussion of the findings presented hitherto, as well as concluding remarks and recommendations for future work in the field.

CHAPTER 8

GENERAL DISCUSSION AND CONCLUSIONS

This chapter will comprise a discussion of (a) the key findings of this thesis, in summarised and integrated form; (b) their significance in light of prior published work; (c) the limitations of the studies described in each chapter; (d) the value of the body of work described in the thesis, and recommendations for future directions in this field with a focus on translational research in LMIC countries such as South Africa; and (e) clearly articulated conclusions.

8.1 Summary of findings

This thesis aimed to investigate a number of questions about trauma and PTSD in the Drakenstein Child Health Study – an ongoing South African birth cohort study. Specific research questions pertained to their prevalence and risk factors in pregnant women, their impact on infant birth anthropometry and development, and their genetic correlations. Five publications addressing these research questions have been included. The key findings of this thesis were as follows:

- (1) Across all studies, psychological trauma (including exposure to childhood trauma, IPV and lifetime trauma) and lifetime PTSD each were found to be highly prevalent – the prevalence of lifetime PTSD was notably higher in this cohort (ranging from 19% to 33% across studies) than has been reported in prior studies such as the SASH (Herman et al. 2009). Recent life stressors were found to be significantly associated with lifetime trauma (when controlling for SES, study site and recent IPV); while childhood trauma and recent stressors were significantly associated with PTSD, controlling for SES and study site. These findings are in line with Hypotheses (a) and (b) of this thesis (see *Chapter 1, Section 1.6 – Study objectives and related publications, p 7*), ie:

Hypothesis (a)

We expected to find a notable prevalence of psychological trauma and of PTSD in this study sample.

Hypothesis (b)

We expected to find significant associations between all or some of the known environmental risk factors, and/or the known stress-related genetic polymorphisms, with the presence of PTSD.

- (2) Maternal trauma exposure was found to increase significantly the risk of poor infant anthropometry at birth. Specifically, mothers who had been exposed to physical IPV during the past year were found to be more likely to deliver an infant with low birthweight (when controlling for study site (clinic), maternal height, ethnicity, SES, substance use and childhood trauma); while those reporting lifetime trauma exposure were found to be at increased risk of delivering an infant with reduced head-circumference-for-age z scores (HCAZ) at birth. This association remained significant when adjusted for study site and recent stressors. These results are in keeping with Hypothesis (c) of this thesis (see *Chapter 1, Section 1.6 – Study objectives and related publications, p 7*), ie:

Hypothesis (c)

We expected to find notable associations between maternal trauma and/or PTSD, and adverse birth and infant outcomes.

- (3) Maternal trauma exposure and PTSD each were found to be significantly associated with poor infant neurodevelopment at age 6 months. Infants born to women reporting a history of past-year sexual IPV exposure were found to have poorer fine motor outcomes, when controlling for clinic site, marital status, SES, depression, PTSD, and tobacco use. Further, maternal PTSD was found to be significantly associated with poorer fine motor and adaptive behaviour (motor) development, with the latter remaining significant when adjusted for site, alcohol dependence, and birth HCAZ score. These findings are thus also in line with Hypothesis (c), as above.

- (4) Among the 33 selected single nucleotide polymorphisms (SNPs) genotyped in this cohort, one SNP in the 3'-untranslated region (3'-UTR) of the regulator of G-protein signaling 2 (*RGS2*) gene, rs4606, was found to be significantly associated with lifetime PTSD after correction for multiple testing. This finding thus confirmed Hypothesis (b) of this thesis, as above.
- (5) Throughout all studies, a number of noteworthy findings were also not consistent with the initial hypotheses; nor with prior work in the field. These discrepancies may have been attributable to multiple factors, including limited power to detect smaller effect sizes; heterogenous assessment of trauma and posttraumatic stress symptomatology; unmeasured (residual) confounding; or temporality of measured risk and outcome variables.

8.2 Significance of findings

8.2.1 Psychological trauma and PTSD: prevalence and risk factors

The findings of this thesis are consistent with a large body of work documenting the high trauma burden in LMIC countries such as South Africa. Gender-based violence is particularly problematic, and presents a notable health risk for women of reproductive age. In their study of 1,395 women attending antenatal clinics in Soweto, South Africa, Dunkle and colleagues (2004b) reported that more than half (55%) of respondents had experienced physical or sexual IPV. This is in keeping with large multi-site studies and reviews of international data (eg. Garcia-Moreno et al. 2006; Krug et al. 2002). The identification of risk factors associated with trauma and IPV may contribute to improved primary prevention, and thus has been of growing interest in recent years. For example, in their systematic review of risk factors in adult and adolescent study samples, Capaldi and colleagues (2012) reported that contextual factors (including low level of education and unemployment); developmental characteristics (eg. exposure to childhood trauma); partner behaviours (eg. poor socio-emotional support); and relationship influences (such as interpersonal discord) all may increase the risk of IPV. Similarly, in their cross-sectional study of a large sample ($n > 1000$) of women aged 18 – 49 years across three South African provinces, Jewkes and colleagues (2002) reported that risk factors for IPV

exposure included prior childhood trauma, low educational level, alcohol consumption and frequent interpersonal conflict. While the analyses in this thesis yielded a significant association between recent life stressors and lifetime trauma exposure, there is a scarcity of published studies investigating specifically the risk factors for psychological trauma in LMIC settings; and further work in this area is warranted.

The prevalence of PTSD in our cohort was found to be notably higher than has been reported in nationally (eg. Herman et al. 2009) and internationally (eg. Kessler et al. 1995, 2005) representative studies. One explanation for this discrepancy may be that the Drakenstein study population is a highly vulnerable cohort, exposed to additional risk factors such as low SES, co-morbid depression and stressful life events. All these may confer increased and cumulative susceptibility to our study participants, when compared to the general population.

In our cohort, exposure to childhood trauma and recent stressors each were found to increase the risk of developing PTSD following traumatic exposure. There is a large body of work detailing the adverse neurobiological effects of childhood trauma and early life stress (eg. Nemeroff 2004; Neigh et al. 2009), which in turn may increase the risk of psychopathological disorders in adulthood (Heim & Nemeroff 2001). In an early cross-sectional study of 1,931 women attending four community-based, primary care internal medicine practices, McCauley and colleagues (1997) found that those women reporting a history of physical or sexual abuse during childhood scored higher on measures of depression and anxiety than did those who reported never having experienced such abuse. Schaaf and McCanne (1998) provided further supporting evidence in their study of the relationship between childhood sexual and/or physical abuse, and adult victimisation and PTSD. In their sample of 475 female college students, these authors found that those participants reporting a history of combined sexual and physical abuse during childhood had significantly higher rates of PTSD and trauma symptoms during adulthood, versus those with no reported history of child abuse. As discussed in *Chapter 3 – Publication 1 (p 38)*, one explanation for the association between childhood trauma and subsequent PTSD in adulthood may be pathophysiological alterations in neurobiological systems of the central nervous system (CNS) due to early life stress or trauma.

8.2.2 Psychological trauma and PTSD: associations with adverse birth outcomes

Our finding of a significant association each between maternal trauma exposure (including IPV) and poor infant birth anthropometry (low birthweight and reduced HCAZ scores) is supported by a notable evidence base. In two recent systematic reviews of birth outcomes among women exposed to IPV (Shah et al. 2010; Boy & Salihu 2004), it was reported that low birthweight and preterm birth each were significantly increased among exposed women, versus those with no reported exposure. Our finding of reduced HCAZ scores in infants of trauma-exposed mothers is also of public health concern, given the suspected association between reduced head circumference at birth and poor health and development in later life (eg. Barker et al. 1993; Wright & Emond 2015).

Importantly, maternal PTSD was not found to be significantly associated with adverse birth outcomes. This is in contrast to one recent prospective three-cohort study (Seng et al. 2011 – see *Chapter 3 – Publication 1, p 25*); and to a large-scale analysis of data from Michigan Medicaid claims between 1994 and 1996 (Seng et al. 2001) showing that 2,219 female recipients of childbearing age had PTSD. In this study, birth outcomes significantly associated with maternal PTSD included ectopic pregnancy, spontaneous abortion and preterm contractions. However, our findings are in line with one large study of the effects of PTSD on pregnancy outcomes (Rogal et al. 2007). In their investigation of 1,100 pregnant women recruited from prenatal clinics in inner-city New Haven, Connecticut, USA, these authors found that while the prevalence of low infant birthweight was 6.5% in their sample, this was not significantly associated with a maternal diagnosis of PTSD during pregnancy (after adjustment for potential confounders). However, the low prevalence of PTSD (3%) in this sample, as well as other methodological limitations, may have biased the results.

8.2.3 Psychological trauma and PTSD: associations with poor infant neurodevelopment

To date, the association between maternal trauma or PTSD and poor infant neurodevelopment has not been studied widely. To the best of our knowledge, this thesis is the first to examine specifically this relationship. A large number of animal and human studies (see eg. Beydoun & Saftlas 2008; Talge et al. 2007; Dunkel Schetter & Tanner 2012; Van den Bergh et al. 2005) have suggested a link between prenatal maternal stress, and disturbed behaviour and development in the offspring. This association likely is underpinned by the foetal programming hypothesis (see Talge et al. 2007), ie. that exposure to a stressful environment in utero can alter foetal development during particularly sensitive periods, thus permanently altering phenotype. It is understood widely that such maternal stress is transmitted to the foetus via two key physiological pathways (Kinsella & Monk 2009; Talge et al. 2007) – *see also Chapter 3 – Publication 1 (p 40)*. First, stress-induced HPA-axis hyperactivity may result in elevated maternal cortisol levels. As approximately 10% to 20% of maternal cortisol is thought to pass transplacentally to the foetus (Gitau et al. 1998; Glover et al. 2009; Kinsella & Monk 2009), this may be above threshold to exert an adverse effect on foetal development. Second, anxiety and stress in pregnancy may be associated with reduced blood flow (high arterial resistance) in the uterine arteries (Teixeira et al. 1999), thus impairing circulation to the foetus. This mechanism may be mediated by sympathetic adrenal activation and increased plasma noradrenaline, as has been demonstrated in early animal studies (eg. Fried & Thoresen 1990). Further work in human study populations would be useful to investigate further this neurobiological mechanism.

8.2.4 PTSD: genetic risk factors and susceptibility

To date, most studies investigating genetic risk factors for PTSD having utilised a candidate gene association approach (see Almli et al. 2014). The selection of most studied genes has been in line with the current neurobiological understanding of PTSD (eg. Heim & Nemeroff 2009), focusing on the HPA-axis, the ascending brainstem locus coeruleus noradrenergic system, and the limbic amygdalar frontal pathway (which mediates fear processing) (Nievergelt et al. 2015) -

see also Chapter 7 – Publication 5 (p 120, 122). It is likely that the overall genetic risk for PTSD comprises small effect-size contributions from a number of individual genetic markers (Rothbaum et al. 2014). Genetic variants which have demonstrated promising associations with PTSD include SNPs of the FKBP5 gene (regulating glucocorticoid receptor sensitivity), which have been found to interact with child abuse severity in predicting PTSD symptoms in adulthood (Binder et al. 2008); CRHR1 (corticotropin releasing hormone type 1 receptor), which mediates stress responses and may be associated with symptoms in hurricane-exposed adults (White et al. 2013); and PACAP (pituitary adenylate cyclase-activating polypeptide), a highly conserved VIP/secretin/glucagon peptide, which regulates the cellular stress response with its PAC1 receptor and has been found to be significantly associated with PTSD in females (Ressler et al. 2011; Vaudry et al. 2009).

Four genome-wide association studies (GWASs) in PTSD have been published to date (see Nievergelt et al. 2015). One focused on European-American (EA) populations (Logue et al. 2013); another looked primarily at African-American (AA) women (Guffanti et al. 2013); the third included both EA and AA individuals (Xie et al. 2013), but only yielded significant signals in the EA sub-population; and the fourth (Nievergelt et al. 2015) comprised a multi-ethnic analysis across multiple ancestries. While a number of novel risk genes for PTSD were implicated in these studies, there is an ongoing need for such large-scale whole-exome studies to be conducted in LMIC countries such as South Africa, in order to elucidate potential susceptibility loci in our unique genetic populations. However, the cost of such innovative approaches is often prohibitively high in these settings. Thus, use of the PsychArray BeadChip (“PsychChip”) - a cost-effective, high-density, GWAS-based microarray – may hold promise for future work in resource-constrained countries (*see Chapter 7 – Publication 5, p 122*).

8.3 Limitations

A number of limitations temper the findings of this thesis. First, despite utilising data from a large birth cohort study, the sample sizes in each sub-analysis were relatively small. Thus, there may have been limited power to detect small, but significant, association effects. Second, the assessment of psychological trauma exposure and lifetime PTSD symptoms in this cohort was dependent largely on participant recall. Thus, intentional or unintentional under-reporting may have biased the results. By the same token, physiological symptoms of pregnancy and the peripartum may have been misattributed by participants to psychopathology, so increasing the risk of false positive diagnoses. Third, while participants were assessed for major depression, this disorder was not included as an outcome measure. Given that PTSD and depression are known to be highly co-morbid (eg. Kessler et al. 1995; Breslau et al. 2000), and may share common genetic liabilities (Sartor et al. 2012), examination of a complex PTSD-depression outcome variable in future studies may be worthwhile. Fourth, the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) used to assess neurodevelopmental outcomes in this cohort have been criticised for their global measurement of milestones, as well as their poor correlation with intelligence tests in later childhood (see Van den Bergh et al. 2005). In future, a more direct assessment of developmental outcomes may be undertaken using neuroimaging techniques and/or neuroendocrine markers. Fifth, the effects of the gender of the index infants were not examined specifically here. As there is some evidence to suggest gender differences in susceptibility to the adverse effects of maternal stress and anxiety (Van den Bergh et al. 2005; García-Cáceres et al. 2010), these data would enhance future analyses. Sixth, while unmeasured confounders may have contributed to our study findings, we attempted to minimise residual confounding by adjusting for key variables such as study site and SES. Finally, the candidate gene approach described in *Chapter 7 – Publication 5 (p 122-123)* is limited inherently by its insufficient coverage of potentially high-risk genes, and its inability to identify new genes without prior knowledge (Amos et al. 2011; Evans et al. 2012).

8.4 Value of the current thesis and recommendations for future work

Despite its limitations, this thesis provides strong evidence for the adverse *sequelae* of psychological trauma and PTSD in a South Africa birth cohort. The inclusion of two sub-populations (Black African, Xhosa-speaking; and Mixed-Race, Afrikaans-speaking) from a poor, peri-urban community, is representative of much of South Africa's sociodemographic composition (SADHS 2003). Examination of these understudied populations with unique ancestries is of utility both to public health and genetic research. Further, consideration of different subtypes of trauma (including childhood trauma and IPV) across varied time periods (eg. recent versus lifetime exposure), as well as important potential confounders (such as depression, substance use and study site), provides a good basis for inferring associations about effects on birth and infant neurodevelopmental outcomes. The higher prevalence of PTSD in this cohort than has been reported previously (eg. Rogal et al. 2007) provided good power to detect significant effects, thus potentially countering the relatively low study sample sizes. The clear distinction between exposure and control groups in these studies also strengthened the tests of association. Finally, inclusion of prospective, longitudinal data allowed an assessment of the transgenerational effects of maternal trauma and PTSD.

In future, further large population-based cohort studies conducted in LMIC settings such as South Africa would be helpful to address the current research gap. As the vast majority of current work focuses on Western, Educated, Industrialised, Rich and Democratic (WEIRD) study populations, there is a need to bolster research in non-WEIRD sites. In particular, more sophisticated genetic approaches, and the inclusion of objective measures such as stress biomarkers and neuroimaging would be beneficial. Intervention studies should be undertaken also to assess (new and existing) pregnancy-specific trauma and PTSD programmes which should be feasible and culturally appropriate. These may include screening for trauma exposure and PTSD symptoms during antenatal appointments (a time during which surveillance and follow-up is routine); psychoeducation of primary care health professionals working with pregnant women and new mothers; and support programmes aimed at reducing maternal stress and anxiety (eg. cognitive-behavioural treatments – Van den Bergh et al. 2005;

Facchinetti et al. 2004). Longitudinal studies of the effects of maternal trauma or PTSD on later child and adolescent health and development would be of value also.

8.5 Conclusions

The key findings of this thesis emphasise that the psychological health of pregnant women and new mothers may have far-reaching consequences on foetal, infant and child well-being.

Improved detection and intervention programmes for trauma and PTSD during pregnancy and the peripartum thus should be an immediate goal in South Africa and other LMIC countries.

Such interventions should be prioritised along with existing initiatives to reduce maternal and child morbidity and mortality. Up-to-date empirical data from LMIC settings such as South Africa are needed not only to inform contextually-appropriate health promotion campaigns, but also to encourage support from governmental sectors and private donors. Ultimately, a focus on the predictors of poor growth and developmental outcomes in infancy and early childhood may be of significant scientific and clinical utility, and may improve long-term individual and societal welfare.

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APPENDIX 1

DSM-5 CRITERIA FOR PTSD

A	<p>Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:</p> <ol style="list-style-type: none">1. Directly experiencing the traumatic event(s).2. Witnessing, in person, the event(s) as it occurred to others.3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). <p>Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.</p>
B	<p>Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:</p> <ol style="list-style-type: none">B1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).B2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).B3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)B4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).B5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
C	<p>Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:</p> <ol style="list-style-type: none">C1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).C2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D	<p>Negative alterations in cognitions and mood that are associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two or more of the following:</p> <p>D1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).</p> <p>D2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., “I am bad,” “No one can be trusted,” “The world is completely dangerous,” “My whole nervous system is permanently ruined”).</p> <p>D3. Persistent distorted cognitions about the cause or consequence of the traumatic event(s) that lead the individual to blame himself/herself or others.</p> <p>D4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).</p> <p>D5. Markedly diminished interest or participation in significant activities.</p> <p>D6. Feeling of detachment or estrangement from others.</p> <p>D7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).</p>
E	<p>Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:</p> <p>E1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.</p> <p>E2. Reckless or self-destructive behavior.</p> <p>E3. Hypervigilance.</p> <p>E4. Exaggerated startle response.</p> <p>E5. Problems with concentration.</p> <p>E6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).</p>
F	<p>Duration of the disturbance (criteria B, C, D, and E) is more than 1 month.</p>
G	<p>The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.</p>
H	<p>The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.</p>
<p>With dissociative symptoms (with either depersonalisation or derealisation).</p> <p>With delayed expression: if the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate)</p>	

APPENDIX 2: QUESTIONNAIRES & ASSESSMENT TOOLS



CRF0X: Socioeconomic Status

Visit: 12 Month 24 Month
 18 Month 30 Month 36 Month

Mother Participant ID: _____

Date: ____/____/____
 DD / MMM / YYYY

Socioeconomic Status			
1	How many children (under 18 years) do you have? Number: _____		
2	How many people normally live in your household, including yourself? (Include people who live there for more than 6 months of the year) Number: _____		
3	How many of these are adults over 18 years? <input type="checkbox"/> No Adults <input type="checkbox"/> 1-3 Adults <input type="checkbox"/> More than 3 adults (Please specify: _____)		
4	How many of these adults over 18 years are women and how many are men? <i>If none over 18, please indicate "0"</i>	4.1	Number of men: _____
		4.2	Number of women: _____
5	How many of these are children aged 5 to 18 years? <i>If none, please write "0"</i> Number: _____		
6	How many of these children aged 5 to 18 years are girls and how many are boys? <i>If none between 5 and 18, please indicate "0"</i>	6.1	Number of girl(s):
		6.2	Number of boy(s):
7	How many of these are children younger than 5 years? <i>If none, please write "0"</i> Number: _____		
8	How many of these children younger than 5 years are girls and how many are boys? <i>If none younger than 5, please indicate "0"</i>	8.1	Number of girl(s):
		8.2	Number of boy(s):
9	What is your relationship to each adult or child living with you at home? <i>Please tick all that apply.</i> <input type="checkbox"/> Your spouse/partner <input type="checkbox"/> Your son or daughter <input type="checkbox"/> Your son-in-law or daughter-in-law <input type="checkbox"/> Your grandchild <input type="checkbox"/> Your parent <input type="checkbox"/> Your parent-in-law <input type="checkbox"/> Your brother or sister <input type="checkbox"/> Your nephew or niece <input type="checkbox"/> Your adopted/foster/step-child <input type="checkbox"/> Other (specify): _____ <input type="checkbox"/> Not related		
10			
11			
12			

CRF0X: Socioeconomic Status



Visit: 12 Month 24 Month
 18 Month 30 Month 36 Month

Mother Participant ID: _____

Date: _____
 DD / MMM / YYYY

13			
14			
15	What is your current employment situation?	<input type="checkbox"/> Working Now <input type="checkbox"/> Self-employed <input type="checkbox"/> Looking for work: Unemployed <input type="checkbox"/> Temporarily Laid Off <input type="checkbox"/> Homemaker <input type="checkbox"/> Student <input type="checkbox"/> Illness/sickness <input type="checkbox"/> Disabled <input type="checkbox"/> Other (please specify): _____	
16	Do you receive any social assistance in the form of a government grant?	<input type="checkbox"/> Yes <input type="checkbox"/> No (if no, skip to Q18)	
17	If yes, what kind of grant do you receive?	<input type="checkbox"/> Childcare grant <input type="checkbox"/> Disability grant <input type="checkbox"/> Care dependency grant	
18	What is your own average income per month (i.e. average over the past 6 months)? <i>(Please tick - your best estimate is fine)</i>	<input type="checkbox"/> Less than R1000 per month <input type="checkbox"/> R1000 – R5000 per month <input type="checkbox"/> R5000 - R10 000 per month <input type="checkbox"/> More than R10 000 per month	
19	What is your average household income per month (i.e. average over the past 6 months)? <i>(Please tick - your best estimate is fine)</i>	<input type="checkbox"/> Less than R1000 per month <input type="checkbox"/> R1000 – R5000 per month <input type="checkbox"/> R5000 – R10000 per month <input type="checkbox"/> R10000 - R15 000 per month <input type="checkbox"/> More than R15 000 per month	
20	Marital Status	20.1	
		<input type="checkbox"/> Single (never been married)	
		<input type="checkbox"/> Not married, but in a marriage like relationship (ie. living together)	If yes, how long have you been living together? _____ months
		<input type="checkbox"/> Married	If yes, how long have you been married? _____ months
		<input type="checkbox"/> Divorced	
		<input type="checkbox"/> Widowed	
21	How many times in your life have you been married and/or lived together with a partner (include current partner if living together)?	20.2	

CRF0X: Socioeconomic Status



Visit: 12 Month 24 Month
 18 Month 30 Month 36 Month

Mother Participant ID: ____/____/____

Date: ____/____/____
 DD / MMM / YYYY

30	How long have you lived at the current address?	_____ years
31	Which of the following best describes your home (type of dwelling)?	<input type="checkbox"/> Shack <input type="checkbox"/> Wendy house or backyard dwelling <input type="checkbox"/> House <input type="checkbox"/> Flat <input type="checkbox"/> Refugee centre/homeless shelter <input type="checkbox"/> Other (specify): _____
32	How many people share your bedroom? <i>Including participant.</i>	Number: _____
33	Which of the following do you have in your home? <i>Please tick all that apply.</i>	<input type="checkbox"/> Electricity <input type="checkbox"/> Tap or running water <input type="checkbox"/> Domestic servant <input type="checkbox"/> A flush toilet inside <input type="checkbox"/> A built-in kitchen sink <input type="checkbox"/> An electric stove or hotplate <input type="checkbox"/> A working telephone (this includes a cell phone) <input type="checkbox"/> At least one motor car or truck <input type="checkbox"/> A motorcycle or scooter <input type="checkbox"/> A bicycle
34	Is the house where you stay owned, rented or an informal settlement plot?	<input type="checkbox"/> Own <input type="checkbox"/> Rent <input type="checkbox"/> Neither, informal settlement plot <input type="checkbox"/> Other (specify): _____
35	Do you own any land other than the land where your house is?	<input type="checkbox"/> Yes <input type="checkbox"/> No
36	Do you personally do any of the following? <i>Please tick all that apply.</i>	<input type="checkbox"/> Shop at supermarkets <input type="checkbox"/> Use any financial services (such as bank account, ATM card or credit card) <input type="checkbox"/> Have an account at a retail store (eg. Pep, Jet etc)

CRF Completed by: _____ Date: ____/____/____
 DD / MMM / YYYY



CRF0X: Planning of the Birth & Partner Support (maternal)

Visit: ANC 2

Mother Participant ID: ____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____

DD / MMM / YYYY

PLANNING OF THE BIRTH & PARTNER SUPPORT																				
1	Was your pregnancy planned?	<input type="checkbox"/> Yes (<i>proceed to Q2</i>) <input type="checkbox"/> No (<i>skip to Q3</i>)																		
2	If yes, by whom?	<input type="checkbox"/> Your spouse/partner <input type="checkbox"/> You <input type="checkbox"/> Both																		
3	Is this baby wanted?	1 No, not at all (<i>skip to Q3.2</i>) 2 Not really (<i>skip to Q3.2</i>) 3 Maybe, a little (<i>proceed to Q3.1</i>) 4 Yes (<i>proceed to Q3.1</i>) 5 Yes, very much indeed (<i>proceed to Q3.1</i>)																		
3.1	If yes, by whom?	<input type="checkbox"/> Your spouse/partner (<i>skip to Q4</i>) <input type="checkbox"/> You (<i>skip to Q4</i>) <input type="checkbox"/> Both (<i>skip to Q4</i>)																		
3.2	If no, does the father of the baby know that you are pregnant?	<input type="checkbox"/> Yes <input type="checkbox"/> No																		
4	Is the father of your child supportive of your pregnancy?	1 Not at all supportive 2 Slightly supportive 3 Moderately supportive 4 Considerably supportive 5 Extremely supportive																		
5	How much can you rely on your partner for help with your pregnancy and your baby?	1 Not at all 2 Slightly/not very often 3 Moderately/some of the time 4 Considerably/most of the time 5 Extremely/all the time																		
6	Have you ever experienced a miscarriage in the past?	<input type="checkbox"/> Yes (<i>if "Yes", proceed to Q7</i>) <input type="checkbox"/> No (<i>if "No", do not answer Q7</i>)																		
7	If yes, how many times (and when)?	<table border="1"> <thead> <tr> <th></th> <th>Miscarriage</th> <th>Year</th> </tr> </thead> <tbody> <tr> <td>7.1</td> <td>Miscarriage 1</td> <td></td> </tr> <tr> <td>7.2</td> <td>Miscarriage 2</td> <td></td> </tr> <tr> <td>7.3</td> <td>Miscarriage 3</td> <td></td> </tr> <tr> <td>7.4</td> <td>If more than 3, how many in total?</td> <td>N/A</td> </tr> <tr> <td></td> <td>_____</td> <td></td> </tr> </tbody> </table> <p><i>For example, if you have suffered two miscarriages in 2002 & 2005, you would fill in 7.1 (2002) and 7.2 (2005) accordingly. 7.3 and 7.4 need not be completed in this case.</i></p>		Miscarriage	Year	7.1	Miscarriage 1		7.2	Miscarriage 2		7.3	Miscarriage 3		7.4	If more than 3, how many in total?	N/A		_____	
	Miscarriage	Year																		
7.1	Miscarriage 1																			
7.2	Miscarriage 2																			
7.3	Miscarriage 3																			
7.4	If more than 3, how many in total?	N/A																		



Visit: ANC 2 7-10 Week 6 Month 12 Month 18 Month 24 Month
 Mother Participant ID: ____/____/____/____ Date: ____/____/____
 Child Participant ID: ____/____/____/____ DD / MMM / YYYY

LIFE EVENTS (LE) QUESTIONNAIRE		
In the past 12 months, did you experience any of the following life events?		
1	A serious illness or injury?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
2	Being the victim of a serious physical attack or assault?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
3	Being robbed or having your home burglarized?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
4	Something valuable being stolen or lost?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
5	The death of anyone close to you?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
6	A separation from your spouse or partner because of marital difficulties?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
7	The break up of any other close relationship?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
8	Being fired from your job?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
9	Retiring from a job when you did not want to?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
10	Losing your job for some other reason?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
11	Unsuccessfully searching for a new job for more than one month?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
12	Are you in a major financial crisis?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
13	Problems with the police?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
14	Did someone very close to you have a serious illness, injury, physical attack or assault?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know

CRF0X: Life Events



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____ DD / MMM / YYYY

In the past 12 months, did you have serious ongoing disagreements or problems getting along with...		
15	Any family members or relatives?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
16	Any close friend?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know
17	Anyone at work?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know

CRF0X: Childhood Trauma Questionnaire (CTQ-SF)



Visit: ANC 2

Mother Participant ID: ____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____

DD / MMM / YYYY

Childhood Trauma Questionnaire – Short Form (CTQ-SF)

Copyright 1996 David P. Bernstein, Ph.D., Laura Fink, Ph.D.

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 to answer as honestly as you can. Your answers will be kept confidential.

	When I was growing up, ...	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 me	1	2	3	4	5
3	People in my family called me things like "stupid", "lazy", 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 or marks.	1	2	3	4	5
12	I was punished with a belt, a board, a cord, 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 someone 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



CRF0X: Intimate Partner Violence

Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____/____ DD/MMM/YYYY

Introduction

In any relationship there are good times and bad times. This questionnaire asks you about some of the bad times you might have had in relationships because we want to learn more about what women experience in their lives. There are no right or wrong answers and anything you say will be kept strictly confidential. Your husband/partner will not be informed that we have asked you these specific questions about your relationship. He will not be asked these same questions, and will not see any of your answers to these questions. Any conversations you might want to have with a study staff member after you have completed this questionnaire - now or at a future clinic visit - will be private.

EMOTIONAL ABUSE									
SCORING for Questions 1-4: 1 = Never 2 = Once 3 = Few 4 = Many <i>Tick the most appropriate answer</i>									
1	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever insulted you or made you feel bad about yourself at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen? <table border="1" style="float: right;"> <tr><td><input type="checkbox"/> 1</td><td>Never</td></tr> <tr><td><input type="checkbox"/> 2</td><td>Once</td></tr> <tr><td><input type="checkbox"/> 3</td><td>Few</td></tr> <tr><td><input type="checkbox"/> 4</td><td>Many</td></tr> </table>	<input type="checkbox"/> 1	Never	<input type="checkbox"/> 2	Once	<input type="checkbox"/> 3	Few	<input type="checkbox"/> 4	Many
<input type="checkbox"/> 1	Never								
<input type="checkbox"/> 2	Once								
<input type="checkbox"/> 3	Few								
<input type="checkbox"/> 4	Many								
2	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever belittled or humiliated you in front of other people at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen? <table border="1" style="float: right;"> <tr><td><input type="checkbox"/> 1</td><td>Never</td></tr> <tr><td><input type="checkbox"/> 2</td><td>Once</td></tr> <tr><td><input type="checkbox"/> 3</td><td>Few</td></tr> <tr><td><input type="checkbox"/> 4</td><td>Many</td></tr> </table>	<input type="checkbox"/> 1	Never	<input type="checkbox"/> 2	Once	<input type="checkbox"/> 3	Few	<input type="checkbox"/> 4	Many
<input type="checkbox"/> 1	Never								
<input type="checkbox"/> 2	Once								
<input type="checkbox"/> 3	Few								
<input type="checkbox"/> 4	Many								
3	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever done things to scare or intimidate you on purpose for example by the way he looked at you, or by yelling and smashing things at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen? <table border="1" style="float: right;"> <tr><td><input type="checkbox"/> 1</td><td>Never</td></tr> <tr><td><input type="checkbox"/> 2</td><td>Once</td></tr> <tr><td><input type="checkbox"/> 3</td><td>Few</td></tr> <tr><td><input type="checkbox"/> 4</td><td>Many</td></tr> </table>	<input type="checkbox"/> 1	Never	<input type="checkbox"/> 2	Once	<input type="checkbox"/> 3	Few	<input type="checkbox"/> 4	Many
<input type="checkbox"/> 1	Never								
<input type="checkbox"/> 2	Once								
<input type="checkbox"/> 3	Few								
<input type="checkbox"/> 4	Many								
4	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever threatened to hurt you at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen? <table border="1" style="float: right;"> <tr><td><input type="checkbox"/> 1</td><td>Never</td></tr> <tr><td><input type="checkbox"/> 2</td><td>Once</td></tr> <tr><td><input type="checkbox"/> 3</td><td>Few</td></tr> <tr><td><input type="checkbox"/> 4</td><td>Many</td></tr> </table>	<input type="checkbox"/> 1	Never	<input type="checkbox"/> 2	Once	<input type="checkbox"/> 3	Few	<input type="checkbox"/> 4	Many
<input type="checkbox"/> 1	Never								
<input type="checkbox"/> 2	Once								
<input type="checkbox"/> 3	Few								
<input type="checkbox"/> 4	Many								



CRF0X: Intimate Partner Violence

Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____ DD/MMM/YYYY

Did you answer "Once", "Few" or "Many" to ANY of these Questions (1-4)?

If so, tick here:

And continue to Question 5.

Did you answer "Never" to ALL of these Questions (1-4)?

If so, tick here:

And skip Question 5, and continue with Question 6.

SCORING for Question 5:
1 = Yes
2 = No

5	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) done any of these things <u>in the past 12 months</u> ?	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	---	---



CRF0X: Intimate Partner Violence

Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____ DD/MMM/YYYY

PHYSICAL ABUSE	
SCORING for Questions 6-10: 1 = Never 2 = Once 3 = Few 4 = Many	
6	<p>Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever slapped you or thrown something at you which could hurt you at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen?</p> <p>1 Never 2 Once 3 Few 4 Many</p>
7	<p>Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever pushed or shoved you at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen?</p> <p>1 Never 2 Once 3 Few 4 Many</p>
8	<p>Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever hit you with a fist or with something else which could hurt you at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen?</p> <p>1 Never 2 Once 3 Few 4 Many</p>
9	<p>Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever kicked, dragged, beaten, choked or burnt you at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen?</p> <p>1 Never 2 Once 3 Few 4 Many</p>
10	<p>Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever threatened to use or actually used a gun, knife or other weapon against you at any point in your lifetime? Did this happen many times, a few times, once or did it not happen?</p> <p>1 Never 2 Once 3 Few 4 Many</p>



CRF0X: Intimate Partner Violence

Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____ DD / MMM / YYYY

Did you answer "Once", "Few" or "Many" to ANY of these Questions (6-10)?

If so, tick here:

And continue to Question 11.

Did you answer "Never" to ALL of these Questions (6-10)?

If so, tick here:

And skip Question 11, and continue with Question 12.

SCORING for Question 11:

1 = Yes

2 = No

11	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) done any of these <u>in the past 12 months</u> ?	1	Yes
		2	No



CRF0X: Intimate Partner Violence

Visit: ANC 2 7-10 Week 6 Month
 12 Month 18 Month 24 Month

Mother Participant ID: _____/_____/_____
 Child Participant ID: _____/_____/_____

Date: ____/____/_____
 DD/MMM/YYYY

SEXUAL ABUSE		
SCORING for Questions 12-14: 1 = Never 2 = Once 3 = Few 4 = Many		
12	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever physically forced you to have sex when you did not want to at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen?	<input type="checkbox"/> 1 Never <input type="checkbox"/> 2 Once <input type="checkbox"/> 3 Few <input type="checkbox"/> 4 Many
13	Have you ever had sex with your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) when you did not want to because you were afraid of what he might do at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen?	<input type="checkbox"/> 1 Never <input type="checkbox"/> 2 Once <input type="checkbox"/> 3 Few <input type="checkbox"/> 4 Many
14	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) ever forced you to do something sexual that you found degrading or humiliating at any point in your lifetime? Did this happen many times, a few times, once, or did it not happen?	<input type="checkbox"/> 1 Never <input type="checkbox"/> 2 Once <input type="checkbox"/> 3 Few <input type="checkbox"/> 4 Many
Did you answer "Once", "Few" or "Many" to <u>ANY</u> of these Questions (12-14)? If so, tick here: <input type="checkbox"/> And continue to Question 15. Did you answer "Never" to <u>ALL</u> of these Questions (12-14)? If so, tick here: <input type="checkbox"/> And skip Question 15, and continue with Question 16.		
SCORING for Question 15: 1 = Yes 2 = No		
15	Has your <u>current or previous</u> intimate partner (for example, your husband, ex-husband, boyfriend or ex-boyfriend) done any of these things <u>in the past 12 months</u> ?	<input type="checkbox"/> 1 Yes <input type="checkbox"/> 2 No

CRF0X: Intimate Partner Violence



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____/____ DD/MMM/YYYY

COMPLETION OF QUESTIONNAIRE	
16	<p>This questionnaire has asked you about many difficult things. How has answering these questions made you feel?</p> <p style="text-align: right;"> <input type="checkbox"/> GOOD/BETTER <input type="checkbox"/> BAD/WORSE <input type="checkbox"/> SAME/NO DIFFERENCE </p>
17	<p>Do you have any comments, or is there anything else you would like to add?</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>
<p>We know these were difficult questions to answer, but it is only by hearing from women themselves that we can really understand about their health and experiences of intimate partner violence. Thank you for helping us, and for taking the time to complete this questionnaire.</p>	
<p>A study staff member will be providing you with a list of organisations that provide support, legal advice and counselling services to women in your area. You can take the information home with you, or leave it at the clinic if you prefer. Please do contact these services if you would like to talk with anyone about your situation. The services are free, and they will keep anything that you say to them private.</p>	



Visit: <input type="checkbox"/> ANC 2	Mother Participant ID: ____/____/____	Date: ____/____/____
	Child Participant ID: ____/____/____	DD / MMM / YYYY

Modified PTSD Symptom Scale (MPSS)
<i>To be completed AFTER completion of the Life Events Questionnaire</i>
INSTRUCTIONS
1. <u>Instruction 1:</u>
After completing the Life Events Questionnaire , please select one event from that questionnaire that involved actual or threatened death or serious injury, or a threat to the physical integrity of yourself or others, and that up to the present has been the most troublesome, disturbing or distressing.
Please write down this event in your own words on the lines below and continue with Instruction 3 (i.e. skip Instruction 2) of this questionnaire.
What type of event was this?

If there was no such event in the Life Events Questionnaire, please tick the box "No such event" and continue with Instruction 2 .
<input type="checkbox"/> No such event (continue with <i>Instruction 2</i>)
2. <u>Instruction 2:</u>
If there was no such event in the Life Events Questionnaire, have you been exposed to any other event in your lifetime that involved actual or threatened death or serious injury, or threat to the physical integrity of yourself or others?
If there was such an event, please write down this event in your own words on the lines below and continue with Instruction 3 of this questionnaire.
What type of event was this?

If there was no such event in your lifetime, please tick the box "No such event":
<input type="checkbox"/> No such event.
IF THERE HAS BEEN NO SUCH EVENT IN YOUR LIFETIME, YOU ARE NOT REQUIRED TO COMPLETE THE REST OF THIS QUESTIONNAIRE. THIS IS THE END OF THE QUESTIONNAIRE FOR YOU.

Visit: ANC 2

Mother Participant ID: ____/____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____/____

DD/MMM/YYYY

3. Instruction 3:

How did you experience the event you have written down? (Please tick one and continue with Instruction 4)

- I experienced the event myself
 I witnessed the event
 I heard of a significant other having experienced the event

4. Instruction 4:

The purpose of the Modified PTSD Symptom Scale (MPSS) is to measure the frequency and severity of symptoms in the past **TWO weeks**. Using the scale listed below, please tick the frequency of symptoms to the right of each item. *Tick only one option.*

FREQUENCY

0 = Not at all

1 = Once per week or less/a little bit/once in a while

2 = Two to four times per week/somewhat/half the time

3 = Five or more times per week/very much/almost always

PLEASE CONTINUE WITH QUESTION 1.

1	Have you had recurrent or intrusive distressing thoughts or recollections about the event(s)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
2	Have you been having recurrent bad dreams or nightmares about the event(s)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
3	Have you had the experience of suddenly reliving the event(s), flashbacks of it, acting or feeling as if it were re-occurring?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always



CRF0X: Modified PTSD Symptom Scale (MPSS)

Visit: ANC 2

Mother Participant ID: ____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____

DD/MM/YY

4	Have you been intensely EMOTIONALLY upset when reminded of the event(s) (includes anniversary reactions)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
5	Have you persistently been making efforts to avoid thoughts or feelings associated with the event(s)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
6	Have you persistently been making efforts to avoid activities, situations, or places that remind you of the event(s)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
7	Are there any important aspects of the event(s) that you still cannot recall?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
8	Have you markedly lost interest in free time activities since the event(s)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always

CRF0X: Modified PTSD Symptom Scale (MPSS)



Visit: ANC 2

Mother Participant ID: ____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____

DD/MMM/YYYY

9	Have you felt detached or cut off from others around you since the event(s)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
10	Have you felt that your ability to experience emotions is less (e.g., unable to have loving feelings, do you feel numb, can't cry when sad, etc.)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
11	Have you felt that any future plans or hopes have changed because of the event(s)? (e.g., no career, marriage, children, or long life?)	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
12	Have you been having persistent difficulty falling or staying asleep?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
13	Have you been continuously irritable or having outbursts of anger?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always



CRF0X: Modified PTSD Symptom Scale (MPSS)

Visit: ANC 2

Mother Participant ID: ____/____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____/____

DD / MMM / YYYY

9	Have you felt detached or cut off from others around you since the event(s)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
10	Have you felt that your ability to experience emotions is less (e.g., unable to have loving feelings, do you feel numb, can't cry when sad, etc.)?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
11	Have you felt that any future plans or hopes have changed because of the event(s)? (e.g., no career, marriage, children, or long life?)	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
12	Have you been having persistent difficulty falling or staying asleep?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always
13	Have you been continuously irritable or having outbursts of anger?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Once per week or less/a little bit/once in a while <input type="checkbox"/> 2 Two to four times per week/somewhat/half the time <input type="checkbox"/> 3 Five or more times per week/very much/almost always

PID:

Date seen:

Translator:

M.I.N.I.

Diagnoses:

Date data entered:

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 6.0.0

DSM-IV

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 6.0.0 (October 10, 2010) (10/10/10)

Fields added for the Drakenstein Child Lung Health Study August 2014

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into modules identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « bold » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➤) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « NO » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question G6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I., please contact:

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e-mail: even-sainteanne@orange.fr

Participant age:

Number of children and ages:

Are you still in a relationship with the father of the (DCLHS) child? YES NO

If so, are you living together? YES NO

Are you married? YES NO

Are you happy in your relationship? YES NO _____

Is your husband/boyfriend working? YES NO

Are you working? YES NO

If the couple are in a relationship, but not living together, ask:

Who do you live with?

Do you all get on well at home? YES NO _____

If there is more than 1 child., ask: Is this man the father of your other child(ren)? YES NO

Ask the following if the father(s) no longer in a relationship with the mother:

If separated or other fathers involved. does the father(s) visit the child(ren)? YES NO

And does he (or do they) provide money to support the child? YES NO

Other comments:

Referral needed? YES NO

Referral to?

Comments:

A. MAJOR DEPRESSIVE EPISODE

➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	a	Were you <u>ever</u> depressed or down, most of the day, nearly every day, for two weeks? IF NO, CODE NO TO A1b: IF YES ASK:	NO	YES	No Yes	No Yes
	b	For the <u>past two weeks</u> , were you depressed or down, most of the day, nearly every day?	NO	YES	No Yes	No Yes
A2	a	Were you <u>ever</u> much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks? IF NO, CODE NO TO A2b: IF YES ASK:	NO	YES	No Yes	No Yes
	b	In the <u>past two weeks</u> , were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time? IF A1a OR A2a CODED YES?	NO	YES	No Yes	No Yes
			➡ NO	YES	No Yes	No Yes

A3 IF A1b OR A2b = YES: EXPLORE THE CURRENT AND THE MOST SYMPTOMATIC PAST EPISODE, OTHERWISE
IF A1b AND A2b = NO: EXPLORE ONLY THE MOST SYMPTOMATIC PAST EPISODE

Over that two week period, when you felt depressed or uninterested:

		Episode 1		Episode 2		Episode 3	
		NO	YES	NO	YES	NO	YES
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by $\pm 5\%$ of body weight or ± 8 lb or ± 3.5 kg, for a 160 lb/70 kg person in a month)? IF YES TO EITHER, CODE YES.						
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning waking or sleeping excessively)?						
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?						
d	Did you feel tired or without energy almost every day?						
e	Did you feel worthless or guilty almost every day? IF YES, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode <input type="checkbox"/> No <input type="checkbox"/> Yes Past Episode <input type="checkbox"/> No <input type="checkbox"/> Yes						
f	Did you have difficulty concentrating or making decisions almost every day?						
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? Did you attempt suicide or plan a suicide? IF YES TO EITHER, CODE YES.						
A4	Did these symptoms cause significant problems at home, at work, socially, at school or in some other important way?						
A5	In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest?						

ARE 5 OR MORE ANSWERS (A1-A3) CODED YES AND IS A4 CODED YES FOR THAT TIME FRAME?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF A5 IS CODED YES, CODE YES FOR RECURRENT.

Age of onset:

NO	YES
MAJOR DEPRESSIVE EPISODE	
CURRENT	<input type="checkbox"/>
PAST	<input type="checkbox"/>
RECURRENT	<input type="checkbox"/>

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

Episode 1:

Episode 2:

Episode 3:

B. SUICIDALITY

Points

In the past month did you:

B1	Have any accident? This includes taking too much of your medication accidentally. IF NO TO B1, SKIP TO B2; IF YES, ASK B1a:	NO	YES	0
B1a	Plan or intend to hurt yourself in any accident either actively or passively (e.g. by not avoiding a risk)? IF NO TO B1a, SKIP TO B2; IF YES, ASK B1b:	NO	YES	0
B1b	Intend to die as a result of any accident?	NO	YES	0
B2	Feel hopeless?	NO	YES	1
B3	Think that you would be better off dead or wish you were dead?	NO	YES	1
B4	Think about hurting or injuring yourself or have mental images of harming yourself, with at least some intent or awareness that you might die as a result?	NO	YES	4
B5	Think about suicide (killing yourself)?	NO	YES	6

IF NO TO B5, SKIP TO B7. OTHERWISE ASK:

Frequency

Intensity

Occasionally	<input type="checkbox"/>	Mild	<input type="checkbox"/>
Often	<input type="checkbox"/>	Moderate	<input type="checkbox"/>
Very often	<input type="checkbox"/>	Severe	<input type="checkbox"/>

B6	Have difficulty restraining yourself from acting on these impulses?	NO	YES	8
B7	Have a suicide method in mind (e.g. how)?	NO	YES	8
B8	Have a suicide plan in mind (e.g. when or where)?	NO	YES	8
B9	Intend to act on thoughts of killing yourself?	NO	YES	8
B10	Intend to die as a result of a suicidal act?	NO	YES	8
B11	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die? This includes times when you were going to kill yourself, but were interrupted or stopped yourself, before harming yourself. IF NO TO B11, SKIP TO B12.	NO	YES	9
B11a	Take active steps to prepare to kill yourself, but you did not start the suicide attempt?	NO	YES	
B11b	Start a suicide attempt, but then you stopped yourself before harming yourself (aborted attempt)?	NO	YES	
B11c	Start a suicide attempt, but then someone or something stopped you before harming yourself (interrupted attempt)?	NO	YES	
B12	Injure yourself on purpose without intending to kill yourself?	NO	YES	4
B13	Attempt suicide (to kill yourself)?	NO	YES	10

A suicide attempt means you did something where you could possibly be injured,
with at least a slight intent to die.

IF NO, SKIP TO B14:

Hope to be rescued / survive

Expected / intended to die

In your lifetime:

Suicide attempt circumstances:

B14 Did you ever make a suicide attempt (try to kill yourself)?

NO

YES

4

"A suicide attempt is any self injurious behavior, with at least some intent (> 0) to die as a result or if intent can be inferred, e.g. if it is clearly not an accident or the individual thinks the act could be lethal, even though denying intent." (C-CASA definition). Posner et al. Am J Psychiatry 164:7, July 2007.

IS AT LEAST 1 OF THE ABOVE (EXCEPT B1) CODED YES?

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (B1-B14)

CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

NO

YES

**SUICIDALITY
CURRENT**

1-8 points Low

9-16 points Moderate

≥ 17 points High

C. MANIC AND HYPOMANIC EPISODES

(➔ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)?

NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER.

IF YES, PLEASE SPECIFY WHO: _____

C1 a Have you ever had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)

NO YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN

BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper'

I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF NO, CODE NO TO C1b: IF YES ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF NO, CODE NO TO C2b: IF YES ASK:

b Are you currently feeling persistently irritable? NO YES

IS C1a OR C2a CODED YES? NO YES

C3 IF C1b OR C2b = YES: EXPLORE THE CURRENT AND THE MOST SYMPTOMATIC PAST EPISODE, OTHERWISE IF C1b AND C2b = NO: EXPLORE ONLY THE MOST SYMPTOMATIC PAST EPISODE

During the times when you felt high, full of energy, or irritable did you:

	Episode 1		Episode 2	
a Feel that you could do things others couldn't do, or that you were an especially important person? <small>IF YES, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA.</small>	NO	YES	NO	YES
<small>Current Episode <input type="checkbox"/> No <input type="checkbox"/> Yes Past Episode <input type="checkbox"/> No <input type="checkbox"/> Yes</small>				
b Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d Have racing thoughts?	NO	YES	NO	YES

	<u>Current Episode</u>		<u>Past Episode</u>	
e Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless?	NO	YES	NO	YES
g Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES
C3 SUMMARY: WHEN RATING CURRENT EPISODE: IF C1b IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES? IF C1b IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?	NO	YES	NO	YES
WHEN RATING PAST EPISODE: IF C1a IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES? IF C1a IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?				
CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.				
RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE C3 SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE C3 SYMPTOMS.				
C4 What is the longest time these symptoms lasted?				
a) 3 days or less		<input type="checkbox"/>		<input type="checkbox"/>
b) 4 to 6 days		<input type="checkbox"/>		<input type="checkbox"/>
c) 7 days or more		<input type="checkbox"/>		<input type="checkbox"/>
C5 Were you hospitalized for these problems?	NO	YES	NO	YES
IF YES, STOP HERE AND CIRCLE YES IN MANIC EPISODE FOR THAT TIME FRAME.				
C6 Did these symptoms cause significant problems at home, at work, socially in your relationships with others, at school or in some other important way?	NO	YES	NO	YES

ARE C3 SUMMARY AND C5 AND C6 CODED YES?

OR

ARE C3 SUMMARY AND C4c AND C6 CODED YES AND IS C5 CODED NO?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO	YES
MANIC EPISODE	
CURRENT	<input type="checkbox"/>
PAST	<input type="checkbox"/>

Episode 1:

Age of onset:

Episode 2

IS C3 SUMMARY CODED YES AND ARE C5 AND C6 CODED NO AND IS EITHER C4b OR C4c CODED YES?

OR

ARE C3 SUMMARY AND C4b AND C6 CODED YES AND IS C5 CODED NO?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF YES TO CURRENT MANIC EPISODE, THEN CODE CURRENT HYPOMANIC EPISODE AS NO.

IF YES TO PAST MANIC EPISODE, THEN CODE PAST HYPOMANIC EPISODE AS NOT EXPLORED.

HYPOMANIC EPISODE

CURRENT	<input type="checkbox"/> NO
	<input type="checkbox"/> YES
PAST	<input type="checkbox"/> NO
	<input type="checkbox"/> YES
	<input type="checkbox"/> NOT EXPLORED

ARE C3 SUMMARY AND C4a CODED YES AND IS C5 CODED NO?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF YES TO CURRENT MANIC EPISODE OR HYPOMANIC EPISODE, THEN CODE CURRENT HYPOMANIC SYMPTOMS AS NO.

IF YES TO PAST MANIC EPISODE OR YES TO PAST HYPOMANIC EPISODE, THEN CODE PAST HYPOMANIC SYMPTOMS AS NOT EXPLORED.

HYPOMANIC SYMPTOMS

CURRENT	<input type="checkbox"/> NO
	<input type="checkbox"/> YES
PAST	<input type="checkbox"/> NO
	<input type="checkbox"/> YES
	<input type="checkbox"/> NOT EXPLORED

C7

a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:

Did you have 2 or more of these (manic) episodes lasting 7 days or more (C4c) in your lifetime (including the current episode if present)?

NO YES

b) IF MANIC OR HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:

Did you have 2 or more of these (hypomanic) episodes lasting just 4 to 6 days (C4b) in your lifetime (including the current episode)?

NO YES

c) IF THE PAST "HYPOMANIC SYMPTOMS" CATEGORY IS CODED POSITIVE ASK:

Did you have these hypomanic symptoms lasting only 1 to 3 days (C4a) 2 or more times in your lifetime, (including the current episode if present)?

NO YES

D. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN D5, D6 AND D7 AND SKIP TO E1)

D1	a	Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack - or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms)?	NO	YES
D4		During the worst attack that you can remember:		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
D5		ARE BOTH D3, AND 4 OR MORE D4 ANSWERS, CODED YES? IF YES TO D5, SKIP TO D7.	NO	YES <small>PANIC DISORDER LIFETIME</small>
D6		IF D5 = NO, ARE ANY D4 ANSWERS CODED YES? THEN SKIP TO E1.	NO	YES <small>LIMITED SYMPTOM ATTACKS LIFETIME</small>

Age of onset:

D7 In the past month, did you have such attacks repeatedly (2 or more), and did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks?

NO YES
PANIC DISORDER
CURRENT

E. AGORAPHOBIA

E1 Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult, like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, or traveling in a bus, train or car or where you might have a panic attack or the panic-like symptoms we just spoke about?

NO YES

IF E1 = NO, CIRCLE NO IN E2.

E2 Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?

Age of onset:

NO YES
AGORAPHOBIA
CURRENT

IS E2 (CURRENT AGORAPHOBIA) CODED YES
and
IS D7 (CURRENT PANIC DISORDER) CODED YES?

NO YES
**PANIC DISORDER
with Agoraphobia
CURRENT**

IS E2 (CURRENT AGORAPHOBIA) CODED NO
and
IS D7 (CURRENT PANIC DISORDER) CODED YES?

NO YES
**PANIC DISORDER
without Agoraphobia
CURRENT**

IS E2 (CURRENT AGORAPHOBIA) CODED YES
and
IS D5 (PANIC DISORDER, LIFETIME) CODED NO?

NO YES
**AGORAPHOBIA, CURRENT
without history of
Panic Disorder**

Agoraphobia comments:

G. OBSESSIVE-COMPULSIVE DISORDER

(➔ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1 In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, or fear or superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, or hoarding, collecting, or religious obsessions.)

NO YES
↓
SKIP TO G4

(DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)

Describe:

G2 Did they keep coming back into your mind even when you tried to ignore or get rid of them?

NO YES
↓
SKIP TO G4

G3 Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?

NO YES
obsessions

G4 In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?

NO YES
compulsions

IS G3 OR G4 CODED YES?

➔
NO YES
➔
NO YES

G5 At any point, did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?

G6 In the past month, did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?

NO YES

**O.C.D.
CURRENT**

Describe compulsions:

Age of onset:

Traumatic events

Event description	Age	Category
		<input type="checkbox"/> Fire/explosion <input type="checkbox"/> Car/train crash <input type="checkbox"/> Other unintentional injury <input type="checkbox"/> Interpersonal violence <input type="checkbox"/> Weapon threat <input type="checkbox"/> Rape <input type="checkbox"/> Attempted rape <input type="checkbox"/> Other sexual <input type="checkbox"/> Illness/injury <input type="checkbox"/> Witnessed unintent injury <input type="checkbox"/> Witnessed violence <input type="checkbox"/> Birth/pregnancy trauma <input type="checkbox"/> Death loved one <input type="checkbox"/> Other
		<input type="checkbox"/> Fire/explosion <input type="checkbox"/> Car/train crash <input type="checkbox"/> Other unintentional injury <input type="checkbox"/> Interpersonal violence <input type="checkbox"/> Weapon threat <input type="checkbox"/> Rape <input type="checkbox"/> Attempted rape <input type="checkbox"/> Other sexual <input type="checkbox"/> Illness/injury <input type="checkbox"/> Witnessed unintent injury <input type="checkbox"/> Witnessed violence <input type="checkbox"/> Birth/pregnancy trauma <input type="checkbox"/> Death loved one <input type="checkbox"/> Other
		<input type="checkbox"/> Fire/explosion <input type="checkbox"/> Car/train crash <input type="checkbox"/> Other unintentional injury <input type="checkbox"/> Interpersonal violence <input type="checkbox"/> Weapon threat <input type="checkbox"/> Rape <input type="checkbox"/> Attempted rape <input type="checkbox"/> Other sexual <input type="checkbox"/> Illness/injury <input type="checkbox"/> Witnessed unintent injury <input type="checkbox"/> Witnessed violence <input type="checkbox"/> Birth/pregnancy trauma <input type="checkbox"/> Death loved one <input type="checkbox"/> Other
		<input type="checkbox"/> Fire/explosion <input type="checkbox"/> Car/train crash <input type="checkbox"/> Other unintentional injury <input type="checkbox"/> Interpersonal violence <input type="checkbox"/> Weapon threat <input type="checkbox"/> Rape <input type="checkbox"/> Attempted rape <input type="checkbox"/> Other sexual <input type="checkbox"/> Illness/injury <input type="checkbox"/> Witnessed unintent injury <input type="checkbox"/> Witnessed violence <input type="checkbox"/> Birth/pregnancy trauma <input type="checkbox"/> Death loved one <input type="checkbox"/> Other
		<input type="checkbox"/> Fire/explosion <input type="checkbox"/> Car/train crash <input type="checkbox"/> Other unintentional injury <input type="checkbox"/> Interpersonal violence <input type="checkbox"/> Weapon threat <input type="checkbox"/> Rape <input type="checkbox"/> Attempted rape <input type="checkbox"/> Other sexual <input type="checkbox"/> Illness/injury <input type="checkbox"/> Witnessed unintent injury <input type="checkbox"/> Witnessed violence <input type="checkbox"/> Birth/pregnancy trauma <input type="checkbox"/> Death loved one <input type="checkbox"/> Other
		<input type="checkbox"/> Fire/explosion <input type="checkbox"/> Car/train crash <input type="checkbox"/> Other unintentional injury <input type="checkbox"/> Interpersonal violence <input type="checkbox"/> Weapon threat <input type="checkbox"/> Rape <input type="checkbox"/> Attempted rape <input type="checkbox"/> Other sexual <input type="checkbox"/> Illness/injury <input type="checkbox"/> Witnessed unintent injury <input type="checkbox"/> Witnessed violence <input type="checkbox"/> Birth/pregnancy trauma <input type="checkbox"/> Death loved one <input type="checkbox"/> Other
		<input type="checkbox"/> Fire/explosion <input type="checkbox"/> Car/train crash <input type="checkbox"/> Other unintentional injury <input type="checkbox"/> Interpersonal violence <input type="checkbox"/> Weapon threat <input type="checkbox"/> Rape <input type="checkbox"/> Attempted rape <input type="checkbox"/> Other sexual <input type="checkbox"/> Illness/injury <input type="checkbox"/> Witnessed unintent injury <input type="checkbox"/> Witnessed violence <input type="checkbox"/> Birth/pregnancy trauma <input type="checkbox"/> Death loved one <input type="checkbox"/> Other

H. POSTTRAUMATIC STRESS DISORDER

(➔ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

H1 Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? ➔
NO YES No Yes No Yes

EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.

H2 Did you respond with intense fear, helplessness or horror? ➔
NO YES No Yes No Yes

H3 During the past month, have you re-experienced the event in a distressing way (such as in dreams, intense recollections, flashbacks or physical reactions) or did you have intense distress when you were reminded about the event or exposed to a similar event? ➔
NO YES No Yes No Yes

H4 In the past month: Event 1 Event 2 Event 3

a Have you avoided thinking about or talking about the event ?	NO YES	NO YES	NO YES
b Have you avoided activities, places or people that remind you of the event?	NO YES	NO YES	NO YES
c Have you had trouble recalling some important part of what happened?	NO YES	NO YES	NO YES
d Have you become much less interested in hobbies or social activities?	NO YES	NO YES	NO YES
e Have you felt detached or estranged from others?	NO YES	NO YES	NO YES
f Have you noticed that your feelings are numbed?	NO YES	NO YES	NO YES
g Have you felt that your life will be shortened or that you will die sooner than other people?	NO YES	NO YES	NO YES
ARE 3 OR MORE H4 ANSWERS CODED YES?	NO YES	➔ NO YES	NO YES

H5 In the past month:	Event 1	Event 2	Event 3
a Have you had difficulty sleeping?	NO YES	NO YES	NO YES
b Were you especially irritable or did you have outbursts of anger?	NO YES	NO YES	NO YES
c Have you had difficulty concentrating?	NO YES	NO YES	NO YES
d Were you nervous or constantly on your guard?	NO YES	NO YES	NO YES
e Were you easily startled?	NO YES	NO YES	NO YES
ARE 2 OR MORE H5 ANSWERS CODED YES?	NO YES	➔ NO YES	NO YES

H6 During the past month, have these problems significantly interfered with your work, school or social activities, or caused significant distress?

NO YES

**POSTTRAUMATIC
STRESS DISORDER
CURRENT**

H7: In your lifetime, have these problems ever lasted for a month or more and significantly interfered with your work, school or social activities, or caused significant distress?
 NO YES (PTSD lifetime)

Age of onset:

I. ALCOHOL DEPENDENCE / ABUSE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

11	In the past 12 months, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?	➡ NO	YES
----	---	---------	-----

12	In the past 12 months:		
a	Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms (for example, "the shakes", sweating or agitation) or to avoid being hungover? <small>IF YES TO ANY, CODE YES.</small>	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	If your drinking caused you health or mental problems, did you still keep on drinking?	NO	YES

ARE 3 OR MORE 12 ANSWERS CODED YES?

⚠ IF YES, SKIP 13 QUESTIONS AND GO TO NEXT MODULE. "DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

Age of onset:

NO	YES [⚠]
ALCOHOL DEPENDENCE CURRENT	

13	In the past 12 months:		
a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? <small>(CODE YES ONLY IF THIS CAUSED PROBLEMS.)</small>	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES

ARE 1 OR MORE 13 ANSWERS CODED YES?

Age of onset:

NO

YES

*ALCOHOL ABUSE
CURRENT*

J. SUBSTANCE DEPENDENCE / ABUSE (NON-ALCOHOL)

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

- | | | | | |
|----|---|---|---------|-----|
| J1 | a | In the past 12 months, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood? | ➡
NO | YES |
|----|---|---|---------|-----|

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicodin, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Phencyclidine: PCP ("Angel Dust", "Peace Pill", "Tranq", "Hog"), or ketamine ("Special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Cough Medicine? Any others?

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS?: _____

FIRST EXPLORE THE DRUG CAUSING THE BIGGEST PROBLEMS AND MOST LIKELY TO MEET DEPENDENCE / ABUSE CRITERIA.

IF MEETS CRITERIA FOR ABUSE OR DEPENDENCE, SKIP TO THE NEXT MODULE. OTHERWISE, EXPLORE THE NEXT MOST PROBLEMATIC DRUG.

- | J2 | Considering your use of (NAME OF DRUG / DRUG CLASS SELECTED), in the past 12 months: | Substance 1 | Substance 2 |
|-----------------------------|--|-------------|-------------|
| a | Have you found that you needed to use much more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it? | NO YES | NO YES |
| b | When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better? | NO YES | NO YES |
| IF YES TO EITHER, CODE YES. | | | |
| c | Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would? | NO YES | NO YES |
| d | Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed? | NO YES | NO YES |
| e | On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or recovering from the drug, or thinking about the drug? | NO YES | NO YES |
| f | Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? | NO YES | NO YES |
| g | If (NAME OF DRUG / DRUG CLASS SELECTED) caused you health or mental problems, did you still keep on using it? | NO YES | NO YES |

Age of onset:

ARE 3 OR MORE J2 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

* IF YES, SKIP J3 QUESTIONS, MOVE TO NEXT DISORDER.
"DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO YES*
SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

J3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem?

NO YES NO YES

(CODE YES ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)?

NO YES NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct?

NO YES NO YES

d if (NAME OF DRUG / DRUG CLASS SELECTED) caused problems with your family or other people, did you still keep on using it?

NO YES NO YES

ARE 1 OR MORE J3 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

Age of onset:

NO YES
SUBSTANCE ABUSE
CURRENT

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

THE PURPOSE OF THIS MODULE IS TO EXCLUDE PATIENTS WITH PSYCHOTIC DISORDERS. THIS MODULE NEEDS EXPERIENCE.

Now I am going to ask you about unusual experiences that some people have.

				BIZARRE	
K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? <small>NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.</small>	NO	YES	YES
	b	IF YES OR YES BIZARRE: do you currently believe these things?	NO	YES	YES ↳K6
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	IF YES OR YES BIZARRE: do you currently believe these things?	NO	YES	YES ↳K6
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? <small>CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.</small>	NO	YES	YES
	b	IF YES OR YES BIZARRE: do you currently believe these things?	NO	YES	YES ↳K6
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspapers, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	IF YES OR YES BIZARRE: do you currently believe these things?	NO	YES	YES ↳K6
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? <small>INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS K1 TO K4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDEUR, JEALOUSY, SIN, KIN OR DESTINY, ETC.</small>	NO	YES	YES
	b	IF YES OR YES BIZARRE: do they currently consider your beliefs strange?	NO	YES	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES	
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES
	b	IF YES OR YES BIZARRE TO K6a: have you heard sounds / voices in the past month?	NO	YES	
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES ↳K6b

K7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES

CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b IF YES: have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

K8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

K9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

K10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

K11 a ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K7a CODED YES OR YES BIZARRE AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST) OR MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED YES?

NO YES
← K13

IF NO TO K11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO K13.

Age of onset:
NO YES
MOOD DISORDER WITH PSYCHOTIC FEATURES
LIFETIME

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM K1a TO K7a) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO K12 AND MOVE TO K13

NO YES
MOOD DISORDER WITH PSYCHOTIC FEATURES
CURRENT

K12 a ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K7b CODED YES OR YES BIZARRE AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT) OR MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED YES?

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO K13 AND K14 AND MOVE TO THE NEXT MODULE.

Comments:

K13 ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K6b, CODED YES BIZARRE?

OR

ARE 2 OR MORE « b » QUESTIONS FROM K1b TO K10b, CODED YES (RATHER THAN YES BIZARRE)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO

YES

**PSYCHOTIC DISORDER
CURRENT**

K14 IS K13 CODED YES

OR

ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K6a, CODED YES BIZARRE?

OR

ARE 2 OR MORE « a » QUESTIONS FROM K1a TO K7a, CODED YES (RATHER THAN YES BIZARRE)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO

YES

**PSYCHOTIC DISORDER
LIFETIME**

Age of onset:

L. ANOREXIA NERVOSA

(➔ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

<p>L1 a How tall are you?</p>	<input type="text"/> ft <input type="text"/> <input type="text"/> in. <input type="text"/> <input type="text"/> <input type="text"/> cm <input type="text"/> <input type="text"/> <input type="text"/> lb <input type="text"/> <input type="text"/> <input type="text"/> kg
<p>b. What was your lowest weight in the past 3 months?</p>	
<p>c. IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)</p>	➔ NO YES

In the past 3 months:

L2 In spite of this low weight, have you tried not to gain weight?	➔ NO YES
L3 Have you intensely feared gaining weight or becoming fat, even though you were underweight?	➔ NO YES
L4 a Have you considered yourself too big / fat or that part of your body was too big / fat?	NO YES
b Has your body weight or shape greatly influenced how you felt about yourself?	NO YES
c Have you thought that your current low body weight was normal or excessive?	NO YES
L5 ARE 1 OR MORE ITEMS FROM L4 CODED YES?	➔ NO YES
L6 FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	➔ NO YES

FOR WOMEN: ARE L5 AND L6 CODED YES?
 FOR MEN: IS L5 CODED YES?

NO	YES
ANOREXIA NERVOSA CURRENT	

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 kg/m²

Age of onset:

Height/Weight	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lb	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kg	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight	5'11	6'0	6'1	6'2	6'3
ft/in	5'11	6'0	6'1	6'2	6'3
lb	125	129	132	136	140
cm	180	183	185	188	191
kg	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m² for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

M. BULIMIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

M1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ NO	YES
M2	In the last 3 months, did you have eating binges as often as twice a week?	➡ NO	YES
M3	During these binges, did you feel that your eating was out of control?	➡ NO	YES
M4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ NO	YES
M5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO	YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO ↓ Skip to M8	YES
M7	Do these binges occur only when you are under (____lb/kg)? <small>INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.</small>	NO	YES

M8 IS M5 CODED YES AND IS EITHER M6 OR M7 CODED NO?

NO	YES
BULIMIA NERVOSA CURRENT	

IS M7 CODED YES?

NO	YES
ANOREXIA NERVOSA Binge Eating/Purging Type CURRENT	

Age of onset:

N. GENERALIZED ANXIETY DISORDER

(➔ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

- | | | | | |
|----|---|---|---------|-----|
| N1 | a | Were you excessively anxious or worried about several routine things, over the past 6 months?
<small>IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a "worry wart"?) AND GET EXAMPLES.</small> | ➔
NO | YES |
| | b | Are these anxieties and worries present most days? | ➔
NO | YES |
| | | ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT? | ➔
NO | YES |

- | | | | |
|----|--|---------|-----|
| N2 | Do you find it difficult to control the worries? | ➔
NO | YES |
|----|--|---------|-----|

- N3 FOR THE FOLLOWING, CODE NO IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.

When you were anxious over the past 6 months, did you, most of the time:

- | | | | |
|---|---|----|-----|
| a | Feel restless, keyed up or on edge? | NO | YES |
| b | Have muscle tension? | NO | YES |
| c | Feel tired, weak or exhausted easily? | NO | YES |
| d | Have difficulty concentrating or find your mind going blank? | NO | YES |
| e | Feel irritable? | NO | YES |
| f | Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning waking or sleeping excessively)? | NO | YES |

ARE 3 OR MORE N3 ANSWERS CODED YES?

- | | | | |
|---|--|----|-----|
| ➔ | | NO | YES |
|---|--|----|-----|

- | | | | |
|----|--|--|--|
| N4 | Do these anxieties and worries disrupt your normal work, school or social functioning or cause you significant distress? | | |
|----|--|--|--|

Comments:

NO YES

GENERALIZED ANXIETY DISORDER CURRENT

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

Age of onset:

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER ASK:

Just before these symptoms began:

- | | | | | |
|-----|---|-----------------------------|------------------------------|------------------------------------|
| O1a | Were you taking any drugs or medicines? | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Uncertain |
| O1b | Did you have any medical illness? | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Uncertain |

IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DISORDER?
IF NECESSARY ASK ADDITIONAL OPEN-ENDED QUESTIONS.

- | | | | | |
|----|---|-----------------------------|------------------------------|------------------------------------|
| O2 | SUMMARY: HAS AN ORGANIC CAUSE BEEN RULED OUT? | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Uncertain |
|----|---|-----------------------------|------------------------------|------------------------------------|

P. ANTISOCIAL PERSONALITY DISORDER

(➔ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO)

- P1 Before you were 15 years old, did you:**
- | | | |
|---|----|-----|
| a repeatedly skip school or run away from home overnight? | NO | YES |
| b repeatedly lie, cheat, "con" others, or steal? | NO | YES |
| c start fights or bully, threaten, or intimidate others? | NO | YES |
| d deliberately destroy things or start fires? | NO | YES |
| e deliberately hurt animals or people? | NO | YES |
| f force someone to have sex with you? | NO | YES |
| ARE 2 OR MORE P1 ANSWERS CODED YES? | NO | YES |

DO NOT CODE YES TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

- P2 Since you were 15 years old, have you:**
- | | | |
|--|----|-----|
| a repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself? | NO | YES |
| b done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)? | NO | YES |
| c been in physical fights repeatedly (including physical fights with your spouse or children)? | NO | YES |
| d often lied or "conned" other people to get money or pleasure, or lied just for fun? | NO | YES |
| e exposed others to danger without caring? | NO | YES |
| f felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property? | NO | YES |

ARE 3 OR MORE P2 QUESTIONS CODED YES?

NO	YES
ANTISOCIAL PERSONALITY DISORDER LIFETIME	

CRF0X: SRQ-20



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____/____ DD / MMM / YYYY

1	Do you often have headaches?	<input type="checkbox"/> YES <input type="checkbox"/> NO
2	Is your appetite poor?	<input type="checkbox"/> YES <input type="checkbox"/> NO
3	Do you sleep badly?	<input type="checkbox"/> YES <input type="checkbox"/> NO
4	Are you easily frightened?	<input type="checkbox"/> YES <input type="checkbox"/> NO
5	Do your hands shake?	<input type="checkbox"/> YES <input type="checkbox"/> NO
6	Do you feel nervous, tense or worried?	<input type="checkbox"/> YES <input type="checkbox"/> NO
7	Is your digestion poor?	<input type="checkbox"/> YES <input type="checkbox"/> NO
8	Do you have trouble thinking clearly?	<input type="checkbox"/> YES <input type="checkbox"/> NO
9	Do you feel unhappy?	<input type="checkbox"/> YES <input type="checkbox"/> NO
10	Do you cry more than usual?	<input type="checkbox"/> YES <input type="checkbox"/> NO
11	Do you find it difficult to enjoy your daily activities?	<input type="checkbox"/> YES <input type="checkbox"/> NO
12	Do you find it difficult to make decisions?	<input type="checkbox"/> YES <input type="checkbox"/> NO
13	Is your daily work suffering?	<input type="checkbox"/> YES <input type="checkbox"/> NO
14	Are you unable to play a useful part in life?	<input type="checkbox"/> YES <input type="checkbox"/> NO
15	Have you lost interest in things?	<input type="checkbox"/> YES <input type="checkbox"/> NO
16	Do you feel that you are a worthless person?	<input type="checkbox"/> YES <input type="checkbox"/> NO



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____/____ DD/MMM/YYYY

17	Has the thought of ending your life been on your mind?	<input type="checkbox"/> YES <input type="checkbox"/> NO
18	Do you feel tired all the time?	<input type="checkbox"/> YES <input type="checkbox"/> NO
19	Do you have uncomfortable feelings in your stomach?	<input type="checkbox"/> YES <input type="checkbox"/> NO
20	Are you easily tired?	<input type="checkbox"/> YES <input type="checkbox"/> NO

CRF0X: Beck Depression Inventory II



Visit: ANC 2

Mother Participant ID: ____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____

DD / MMM / YYYY

Instructions:	
This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling in the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).	
1	Sadness
0	I do not feel sad
1	I feel sad much of the time
2	I feel sad all of the time
3	I am so sad or unhappy that I can't stand it.
2	Pessimism
0	I am not discouraged about my future.
1	I feel more discouraged about my future than I used to be.
2	I do not expect things to work out for me.
3	I feel my future is hopeless and will only get worse.
3	Past Failure
0	I do not feel like a failure.
1	I have failed more than I should have.
2	As I look back, I see a lot of failures.
3	I feel I am a total failure as a person.
4	Loss of Pleasure
0	I get as much pleasure as I ever did from the things I enjoy.
1	I don't enjoy things as much as I used to.
2	I get very little pleasure from the things I used to enjoy.
3	I can't get any pleasure from the things I used to enjoy.
5	Guilty Feelings
0	I don't feel particularly guilty.
1	I feel guilty over many things I have done or should have done.
2	I feel quite guilty most of the time.
3	I feel guilty all of the time.
6	Punishment Feelings
0	I don't feel I am being punished.
1	I feel I may be punished.
2	I expect to be punished.
3	I feel I am being punished.
7	Self-Dislike
0	I feel the same about myself as ever.
1	I have lost confidence in myself.
2	I am disappointed in myself.
3	I dislike myself.



CRF0X: Beck Depression Inventory II

Visit: ANC 2

Mother Participant ID: ____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____

DD / MMM / YYYY

8	Self-Criticalness
0	I don't criticize or blame myself more than usual.
1	I am more critical of myself than I used to be.
2	I criticize myself for all my faults.
3	I blame myself for everything bad that happens.
9	Suicidal Thoughts or Wishes
0	I don't have any thoughts of killing myself.
1	I have thoughts of killing myself, but I would not carry them out.
2	I would like to kill myself.
3	I would kill myself if I had the chance.
10	Crying
0	I don't cry any more than I used to.
1	I cry more than I used to.
2	I cry over every little thing.
3	I feel like crying, but I can't.
11	Agitation
0	I am no more restless or wound up than usual.
1	I feel more restless or wound up than usual.
2	I am so restless or agitated that it's hard to stay still.
3	I am so restless or agitated that I have to keep moving or doing something.
12	Loss of Interest
0	I have not lost interest in other people or activities.
1	I am less interested in other people or things than before.
2	I have lost most of my interest in other people or things.
3	It's hard to get interested in anything.
13	Indecisiveness
0	I make decisions about as well as ever.
1	I find it more difficult to make decisions than usual.
2	I have much greater difficulty in making decisions than I used to.
3	I have trouble making any decisions.
14	Worthlessness
0	I do not feel I am worthless.
1	I don't consider myself as worthwhile and useful as I used to be.
2	I feel more worthless as compared to other people.
3	I feel utterly worthless.
15	Loss of Energy
0	I have as much energy as ever.
1	I have less energy than I used to have.
2	I don't have enough energy to do very much.
3	I don't have enough energy to do anything.
16	Changes in Sleeping Pattern
0	I have not experienced any change in my sleeping pattern.
1a	I sleep somewhat more than usual.
1b	I sleep somewhat less than usual.
2a	I sleep a lot more than usual.
2b	I sleep a lot less than usual.
3a	I sleep most of the day.
3b	I wake up 1-2 hours early and can't get back to sleep.

CRF0X: Beck Depression Inventory II



Visit: ANC 2

Mother Participant ID: ____/____/____

Date: ____/____/____

Child Participant ID: ____/____/____

DD / MMM / YYYY

17	Irritability
0	I am no more irritable than usual.
1	I am more irritable than usual.
2	I am much more irritable than usual.
3	I am irritable all the time.
18	Changes in Appetite
0	I have not experienced any change in my appetite.
1a	My appetite is somewhat less than usual.
1b	My appetite is somewhat greater than usual.
2a	My appetite is much less than before.
2b	My appetite is much greater than usual.
3a	I have no appetite at all.
3b	I crave food all the time.
19	Concentration Difficulty
0	I can concentrate as well as ever.
1	I can't concentrate as well as usual.
2	It's hard to keep my mind on anything for very long.
3	I find I can't concentrate on anything.
20	Tiredness or Fatigue
0	I am no more tired or fatigued than usual.
1	I get more tired or fatigued more easily than usual.
2	I am too tired or fatigued to do a lot of things I used to do.
3	I am too tired or fatigued to do most of the things I used to do.
21	Loss of Interest in Sex
0	I have not noticed any recent change in my interest in sex.
1	I am less interested in sex than I used to be.
2	I am much less interested in sex now.
3	I have lost interest in sex completely.

CRF0X: Edinburgh Post-Natal Depression Scale (EPDS) (maternal)



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____ DD / MM / YYYY

Address		
Phone Number		
<p>As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.</p> <p>Example:</p> <p>Here is an example, already completed. I have felt happy:</p> <p><input type="checkbox"/> Yes, all the time <input checked="" type="checkbox"/> Yes, most of the time <input type="checkbox"/> No, not very often <input type="checkbox"/> No, not at all</p> <p><i>This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.</i></p>		
IN THE PAST 7 DAYS:		
1	I have been able to laugh and see the funny side of things	<input type="checkbox"/> As much as I always could <input type="checkbox"/> Not quite so much now <input type="checkbox"/> Definitely not so much now <input type="checkbox"/> Not at all
2	I have looked forward with enjoyment to things	<input type="checkbox"/> As much as I ever did <input type="checkbox"/> Rather less than I used to <input type="checkbox"/> Definitely less than I used to <input type="checkbox"/> Hardly at all
3*	I have blamed myself unnecessarily when things went wrong	<input type="checkbox"/> Yes, most of the time <input type="checkbox"/> Yes, some of the time <input type="checkbox"/> Not very often <input type="checkbox"/> No, never
4	I have been anxious or worried for no good reason	<input type="checkbox"/> No, not at all <input type="checkbox"/> Hardly ever <input type="checkbox"/> Yes, sometimes <input type="checkbox"/> Yes, very often
5*	I have felt scared or panicky for no very good reason	<input type="checkbox"/> Yes, quite a lot <input type="checkbox"/> Yes, sometimes <input type="checkbox"/> No, not much <input type="checkbox"/> No, not at all

CRF0X: Edinburgh Post-Natal Depression Scale (EPDS) (maternal)



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____/____ Date: ____/____/____
 13 Month 18 Month 24 Month Child Participant ID: ____/____/____/____ DD/ MMM/ YYYY

6*	Things have been getting on top of me	<input type="checkbox"/> Yes, most of the time I haven't been able to cope at all <input type="checkbox"/> Yes, sometimes I haven't been coping as well as usual <input type="checkbox"/> No, most of the time I have coped quite well <input type="checkbox"/> No, I have been coping as well as ever
7*	I have been so unhappy that I have had difficulty sleeping	<input type="checkbox"/> Yes, most of the time <input type="checkbox"/> Yes, sometimes <input type="checkbox"/> Not very often <input type="checkbox"/> No, never
8*	I have felt sad or miserable	<input type="checkbox"/> Yes, most of the time <input type="checkbox"/> Yes, quite often <input type="checkbox"/> Not very often <input type="checkbox"/> No, not at all
9*	I have been so unhappy that I have been crying	<input type="checkbox"/> Yes, most of the time <input type="checkbox"/> Yes, quite often <input type="checkbox"/> Only occasionally <input type="checkbox"/> No, never
10*	The thought of harming myself has occurred to me	<input type="checkbox"/> Yes, quite often <input type="checkbox"/> Sometimes <input type="checkbox"/> Hardly ever <input type="checkbox"/> Never

QUESTIONS 1, 2, & 4
 Are scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3.

QUESTIONS 3, 5 - 10
 (marked with an *)
 Are reverse scored, with the top box scored as a 3 and the bottom box scored as 0.

Maximum score: 30
 Possible Depression: 10 or greater (*mothers*); 8 or greater (*fathers*)
 Always look at item 10 (suicidal thoughts)



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: _____/_____/_____/_____
 12 Month 18 Month 24 Month Child Participant ID: _____/_____/_____/_____
Date: ____/____/_____
DD/MM/YY

ASSIST QUESTIONNAIRE – WHO

These are some questions about your experience of using substances across your lifetime and in the past three months. These substances can be smoked, swallowed, snorted, inhaled, injected or taken in the form of pills. Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, pain medications). For these questions, do not record medications that are used as prescribed by your doctor. However, if you have taken such medications for reasons other than prescription, or taken them more frequently or at higher doses than prescribed, please record these. While we are also interested in knowing about your use of various illicit (illegal) drugs, please be assured that information on such use will be treated as confidential.

I	In your life, which of the following substances have you ever used? (NON-MEDICAL USE ONLY)	NO	YES
A	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3
B	Alcoholic beverages (beer, wine, spirits, etc.)	0	3
C	Cannabis (marijuana, pot, grass, hash, dagga, etc.)	0	3
D	Cocaine (coke, crack, etc.)	0	3
E	Amphetamine-type stimulants (speed, diet pills, ecstasy, Tik, etc.)	0	3
F	Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3
G	Sedatives or Sleeping Pills (Valium, Serenax, Rohypnol, etc.)	0	3
H	Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3
I	Opioids (heroin, morphine, methadone, codeine, etc.)	0	3
J	Other – specify:	0	3
If all answers are negative: "Not even when you were in school?"		If "No" to all items, do not continue with this questionnaire. If "Yes" to any of these items, answer Question 2 for each substance ever used.	

2	In the past three months, how often have you used the substances you mentioned (FIRST DRUG, SECOND DRUG, ETC)?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
A	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	2	3	4	6
B	Alcoholic beverages (beer, wine, spirits, etc.)	0	2	3	4	6
C	Cannabis (marijuana, pot, grass, hash, dagga, etc.)	0	2	3	4	6
D	Cocaine (coke, crack, etc.)	0	2	3	4	6
E	Amphetamine-type stimulants (speed, diet pills, ecstasy, Tik, etc.)	0	2	3	4	6
F	Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	2	3	4	6
G	Sedatives or Sleeping Pills (Valium, Serenax, Rohypnol, etc.)	0	2	3	4	6
H	Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	2	3	4	6
I	Opioids (heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
J	Other – specify:	0	2	3	4	6
If "Never" to all items in Question 2, skip to Question 6. If any substances in Question 2 were used in the previous three months, continue with Question 3, 4 & 5 for each substance used.						

CRF0X: ASSIST



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: _____ / ____ / ____ Date: ____ / ____ / ____
 12 Month 18 Month 24 Month Child Participant ID: _____ / ____ / ____ DD / MMM / YYYY

3	During the <u>past three months</u> , how often have you had a strong desire or urge to use <i>(FIRST DRUG, SECOND DRUG, ETC)</i> ?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
A	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3	4	5	6
B	Alcoholic beverages (beer, wine, spirits, etc.)	0	3	4	5	6
C	Cannabis (marijuana, pot, grass, hash, dagga, etc.)	0	3	4	5	6
D	Cocaine (coke, crack, etc.)	0	3	4	5	6
E	Amphetamine-type stimulants (speed, diet pills, ecstasy, Tik, etc.)	0	3	4	5	6
F	Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3	4	5	6
G	Sedatives or Sleeping Pills (Valium, Serenax, Rohypnol, etc.)	0	3	4	5	6
H	Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3	4	5	6
I	Opioids (heroin, morphine, methadone, codeine, etc.)	0	3	4	5	6
J	Other - specify:	0	3	4	5	6

4	During the <u>past three months</u> , how often has your use of <i>(FIRST DRUG, SECOND DRUG, ETC)</i> led to health, social, legal or financial problems?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
A	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	4	5	6	7
B	Alcoholic beverages (beer, wine, spirits, etc.)	0	4	5	6	7
C	Cannabis (marijuana, pot, grass, hash, dagga, etc.)	0	4	5	6	7
D	Cocaine (coke, crack, etc.)	0	4	5	6	7
E	Amphetamine-type stimulants (speed, diet pills, ecstasy, Tik, etc.)	0	4	5	6	7
F	Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	4	5	6	7
G	Sedatives or Sleeping Pills (Valium, Serenax, Rohypnol, etc.)	0	4	5	6	7
H	Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	4	5	6	7
I	Opioids (heroin, morphine, methadone, codeine, etc.)	0	4	5	6	7
J	Other - specify:	0	4	5	6	7

5	During the <u>past three months</u> , how often have you failed to do what was normally expected of you because of your use of <i>(FIRST DRUG, SECOND DRUG, ETC)</i> ?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
A	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	5	6	7	8
B	Alcoholic beverages (beer, wine, spirits, etc.)	0	5	6	7	8
C	Cannabis (marijuana, pot, grass, hash, dagga, etc.)	0	5	6	7	8
D	Cocaine (coke, crack, etc.)	0	5	6	7	8
E	Amphetamine-type stimulants (speed, diet pills, ecstasy, Tik, etc.)	0	5	6	7	8
F	Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	5	6	7	8
G	Sedatives or Sleeping Pills (Valium, Serenax, Rohypnol, etc.)	0	5	6	7	8
H	Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	5	6	7	8
I	Opioids (heroin, morphine, methadone, codeine, etc.)	0	5	6	7	8
J	Other - specify:	0	5	6	7	8

CRF0X: ASSIST



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____ DD/MM/YYYY

Answer Questions 6 & 7 for all substances ever used (i.e. those endorsed in Question 1)

6	Has a friend or relative or anyone else ever expressed concern about your use of (FIRST DRUG, SECOND DRUG, ETC)?	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
A	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
B	Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
C	Cannabis (marijuana, pot, grass, hash, dagga, etc.)	0	6	3
D	Cocaine (coke, crack, etc.)	0	6	3
E	Amphetamine-type stimulants (speed, diet pills, ecstasy, Tik, etc.)	0	6	3
F	Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
G	Sedatives or Sleeping Pills (Valium, Serenax, Rohypnol, etc.)	0	6	3
H	Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
I	Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
J	Other - specify:	0	6	3

7	Have you ever tried and failed to control, cut down or stop using (FIRST DRUG, SECOND DRUG, ETC)?	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
A	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
B	Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
C	Cannabis (marijuana, pot, grass, hash, dagga, etc.)	0	6	3
D	Cocaine (coke, crack, etc.)	0	6	3
E	Amphetamine-type stimulants (speed, diet pills, ecstasy, Tik, etc.)	0	6	3
F	Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
G	Sedatives or Sleeping Pills (Valium, Serenax, Rohypnol, etc.)	0	6	3
H	Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
I	Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
J	Other - specify:	0	6	3

8	Have you ever used any drug by injection? (NON-MEDICAL USE ONLY)	<input type="checkbox"/> No, never <input type="checkbox"/> Yes, in the past 3 months <input type="checkbox"/> Yes, but not in the past 3 months
---	--	--



Visit: ANC 2 7-10 Week 6 Month Mother Participant ID: ____/____/____/____ Date: ____/____/____
 12 Month 18 Month 24 Month Child Participant ID: ____/____/____/____ DD/MM/ YYYY

IMPORTANT NOTE

If you have injected drugs in the last 3 months, please indicate your pattern of injecting during this period (below):



SCORING GUIDELINES

For each substance (labeled A to J) add up the scores received for questions 2 through 7 inclusive. Do not include the results from either Q1 or Q8 in this score. For example, a score for cannabis would be calculated as: Q2c + Q3c + Q4c + Q5c + Q6c + Q7c

Note that Q5 for tobacco is not coded, and is calculated as: Q2a + Q3a + Q4a + Q6a + Q7a

	Record specific substance score	No intervention	Receive brief intervention	More intensive treatment
a) Tobacco		0-3	4-26	27+
b) Alcohol		0-10	11-26	27+
c) Cannabis		0-3	4-26	27+
d) Cocaine		0-3	4-26	27+
e) Amphetamine		0-3	4-26	27+
f) Inhalants		0-3	4-26	27+
g) Sedatives		0-3	4-26	27+
h) Hallucinogens		0-3	4-26	27+
i) Opioids		0-3	4-26	27+
j) Other drugs		0-3	4-26	27+

Scoring: Count up questions 2-7

- Total Drug 1: _____ (name of drug) _____ (score)
- Total Drug 2: _____ (name of drug) _____ (score)
- Total Drug 3: _____ (name of drug) _____ (score)
- Total Drug 4: _____ (name of drug) _____ (score)

CRF0X: Maternal Respiratory & Medical Enrollment Form



Visit: Enrolment

Mother Participant ID: ____/____/____

Date: ____/____/____
DD / MMM / YYYY

PREGNANCY & CURRENT CONDITION		
1	When was your last menstrual period?	____/____/____ DD / MMM / YYYY
2	When is your expected date of delivery?	____/____/____ DD / MMM / YYYY
3	Are you currently well?	<input type="checkbox"/> Yes <input type="checkbox"/> No
4	Has a doctor or nurse told you that you have any of the following health problem/s during this pregnancy? <i>Tick all that apply.</i>	<input type="checkbox"/> Asthma <input type="checkbox"/> TB <input type="checkbox"/> Emphysema <input type="checkbox"/> Chronic Bronchitis <input type="checkbox"/> Pneumonia <input type="checkbox"/> Cold/Flu <input type="checkbox"/> Excessive vomiting <input type="checkbox"/> Diabetes <input type="checkbox"/> High blood pressure/eclampsia/pre-eclampsia <input type="checkbox"/> Pelvic inflammatory disease <input type="checkbox"/> Heart problem <input type="checkbox"/> Depression <input type="checkbox"/> HIV <input type="checkbox"/> Urine Infection <input type="checkbox"/> Other (specify): _____
5	Are you currently taking medication or was medication prescribed today? + <i>If yes, record in medication chart.</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
6	At the time you became pregnant, were you using any family planning?	<input type="checkbox"/> Yes <input type="checkbox"/> No
7	At the time you became pregnant, were you trying to have a baby?	<input type="checkbox"/> Yes <input type="checkbox"/> No

CRF0X: Maternal Respiratory & Medical Enrollment Form



Visit: Enrolment

Mother Participant ID: ____/____/____

Date: ____/____/____
DD / MMM / YYYY

Please fill in the following information for mother's previous pregnancies: (*Data abstraction from ANC card*). For "sex" record F or M. For "status" A=alive, NND = Neonatal death; ID = Infant death; IUD = Intra-uterine death. If no previous children, write "N/A"

	(A) Year	(B) Gestation	(C) Delivery	(D) Weight	(E) Sex	(F) Status
8		FT / Prem	NVD / CS		M / F	A / NND / ID / IUD
9		FT / Prem	NVD / CS		M / F	A / NND / ID / IUD
10		FT / Prem	NVD / CS		M / F	A / NND / ID / IUD
11		FT / Prem	NVD / CS		M / F	A / NND / ID / IUD
12		FT / Prem	NVD / CS		M / F	A / NND / ID / IUD
13		FT / Prem	NVD / CS		M / F	A / NND / ID / IUD

CLINICAL SERVICE USE	
14	Have you attended any sessions at the antenatal clinic (ANC)? <input type="checkbox"/> Yes <input type="checkbox"/> No
15	If yes, what was the date of your first ANC visit? ____/____/____ DD / MMM / YYYY
16	Have you been tested for HIV? <i>If not, please refer for HIV testing</i> <input type="checkbox"/> Yes↓ <input type="checkbox"/> No (if no, skip to Q21)
17	Are you HIV positive? <input type="checkbox"/> Yes↓ <input type="checkbox"/> No (if no, skip to Q21) <input type="checkbox"/> Don't know
18	When did you first become aware of your HIV status? <input type="checkbox"/> During this pregnancy <input type="checkbox"/> Before this pregnancy
19	Are you currently taking ARVs? <input type="checkbox"/> Yes <input type="checkbox"/> No
20	If yes, what are you currently taking? + <i>Record in medication chart.</i> <input type="checkbox"/> AZT only <input type="checkbox"/> HAART <input type="checkbox"/> Other (specify):
21	What supplements are you taking? + <i>Record in medication chart.</i> <input type="checkbox"/> Multivitamins <input type="checkbox"/> Zinc <input type="checkbox"/> Other (specify):

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22	Have any of your children died?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q29)						
23	How many of your children have died?	Number:						
	What was the main sickness or reason which led to death for the child(ren) you have lost? <i>Tick ALL appropriate reasons for each child that has died.</i>		A	B	C	D	E	F
		Child	Diarrhoea	Pneumonia	HIV	Accident	Unknown	Other
24		1						
25		2						
26		3						
27		4						
28	5							

PAST ILLNESS

	Have you EVER been told by a doctor or nurse that you have any of the following? <i>Circle answer.</i>	
	Condition	Yes/No/Don't Know
29	Chest infection/pneumonia	Y / N / DK
30	Bronchitis/COPD	Y / N / DK
31	Emphysema	Y / N / DK
32	TB	Y / N / DK
33	If Yes, how many TB episodes have you ever been treated for? Number: _____	
34	Osteoporosis or soft bones	Y / N / DK
35	Blood clot	Y / N / DK
36	A joint disorder e.g. arthritis, gout	Y / N / DK
37	Diabetes (blood sugar)	Y / N / DK
38	Epilepsy/fits	Y / N / DK
39	Depression requiring medication	Y / N / DK
40	Stroke	Y / N / DK
41	Cancer	Y / N / DK
42	Heart attack or angina	Y / N / DK
43	Other heart disease	Y / N / DK
44	High blood pressure	Y / N / DK

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45	Have you been admitted to hospital in the past 2 years?	<input type="checkbox"/> Yes↓ <input type="checkbox"/> No (Go to Q49)		
If Yes, please specify details of these hospital admissions (most recent first):				
		A Date	B Where	C What for?
46	Admission 1	DD / MMM / YYYY 	<input type="checkbox"/> Paarl Hospital <input type="checkbox"/> Tygerburg Hospital <input type="checkbox"/> Jooste Hospital <input type="checkbox"/> Other (specify): _____ _____	<input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchitis <input type="checkbox"/> TB <input type="checkbox"/> High blood pressure <input type="checkbox"/> Stroke <input type="checkbox"/> Kidney problems <input type="checkbox"/> Trauma/accident <input type="checkbox"/> Asthma <input type="checkbox"/> Other (specify): _____
47	Admission 2	DD / MMM / YYYY 	<input type="checkbox"/> Paarl Hospital <input type="checkbox"/> Tygerburg Hospital <input type="checkbox"/> Jooste Hospital <input type="checkbox"/> Other (specify): _____ _____	<input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchitis <input type="checkbox"/> TB <input type="checkbox"/> High blood pressure <input type="checkbox"/> Stroke <input type="checkbox"/> Kidney problems <input type="checkbox"/> Trauma/accident <input type="checkbox"/> Asthma <input type="checkbox"/> Other (specify): _____
48	Admission 3	DD / MMM / YYYY 	<input type="checkbox"/> Paarl Hospital <input type="checkbox"/> Tygerburg Hospital <input type="checkbox"/> Jooste Hospital <input type="checkbox"/> Other (specify): _____ _____	<input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchitis <input type="checkbox"/> TB <input type="checkbox"/> High blood pressure <input type="checkbox"/> Stroke <input type="checkbox"/> Kidney problems <input type="checkbox"/> Trauma/accident <input type="checkbox"/> Asthma <input type="checkbox"/> Other (specify): _____

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RESPIRATORY SYMPTOMS		
Do you currently have any of the following? <i>Circle answer.</i>		
Respiratory Symptoms	Yes/No	Duration (number of days, today=1)
49 Wheezing	Y / N	
50 Tightness in your chest	Y / N	
51 Shortness of breath	Y / N	
52 Coughing	Y / N	
53 Phlegm on the chest	Y / N	
54 Night sweats	Y / N	
55 Fever	Y / N	
56 Tiredness	Y / N	
57 Loss of appetite	Y / N	
58 Weight loss	Y / N	
59 Vomiting	Y / N	

WHEEZE AND TIGHTNESS IN CHEST		
60	Have you ever had a whistling or wheezing noise in your chest?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q67)
61	During the last 12 months have you had wheezing or tightness of your chest?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q67)
62	Were you also short of breath?	<input type="checkbox"/> Yes <input type="checkbox"/> No
63	Do you usually get wheezing when you have a cold?	<input type="checkbox"/> Yes <input type="checkbox"/> No
64	When you do not have a cold, do you get wheezing, difficult breathing or a tight chest?	<input type="checkbox"/> Yes <input type="checkbox"/> No
65	Is your sleep ever interrupted by wheezing or a tight chest?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (Q67)
66	If Yes, has this occurred in the last 12 months?	<input type="checkbox"/> Yes <input type="checkbox"/> No

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SHORTNESS OF BREATH		
67	Have you ever had an attack of shortness of breath when you were at rest?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (Go to Q70)
68	If Yes, has this occurred in the last 12 months?	<input type="checkbox"/> Yes <input type="checkbox"/> No
69	Are you more short of breath when exercising compared to other people your age?	<input type="checkbox"/> Yes <input type="checkbox"/> No

COUGH AND PHLEGM		
70	Do you currently have a cough on most days?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q79)
71	When you cough, do you usually bring up phlegm from your chest?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q74)
72	Have you brought up phlegm every day for at least three months during the last year?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q74)
73	How many years have you brought up phlegm in this way?	Years: _____
74	Have you been woken by an attack of coughing in the last 12 months?	<input type="checkbox"/> Yes <input type="checkbox"/> No
75	Do you usually cough when you get up in the morning?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to 77)
76	If Yes, does this occur on most mornings for at least three months in a row each year?	<input type="checkbox"/> Yes <input type="checkbox"/> No
77	Do you easily bring up phlegm from your chest when you get up in the morning?	<input type="checkbox"/> Yes <input type="checkbox"/> No
78	Have you been woken by an attack of coughing when you did not have a cold in the last 12 months?	<input type="checkbox"/> Yes <input type="checkbox"/> No

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BREATHING		
79	Do you ever have trouble breathing?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q85)
80	If Yes, how often do you have this trouble?	<input type="checkbox"/> Continuously (your breathing is never quite right) <input type="checkbox"/> Repeatedly (but it always gets completely better between episodes) <input type="checkbox"/> Rarely (less than once a month)
81	Are you troubled by shortness of breath when walking fast or walking up a hill?	<input type="checkbox"/> Yes <input type="checkbox"/> No
82	Have you ever been troubled by coughing a lot when you run or just after you have stopped running?	<input type="checkbox"/> Yes <input type="checkbox"/> No
83	Does cold air make you cough a lot?	<input type="checkbox"/> Yes <input type="checkbox"/> No
84	Do you sometimes cough in bed at night when you do not have a cold?	<input type="checkbox"/> Yes <input type="checkbox"/> No

ASTHMA AND WHEEZING		
85	Have you ever had asthma?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (Go to 93)
86	How many days in the last twelve months was your asthma or wheezing so severe that you couldn't do your daily activities or go to work?	Number of days: _____
87	Have you had treatment for asthma in the last year?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (Go to 89)
88	If yes, what was the treatment: _____ + Record in medication chart.	
89	Have you ever received treatment at an emergency department for asthma or wheezing?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (Go to 91)

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90	If Yes, how many times in the past year?	<input type="checkbox"/> 1-2 <input type="checkbox"/> 3-5 <input type="checkbox"/> 6-10 <input type="checkbox"/> >10
91	Have you ever been admitted (slept in hospital) for asthma or wheezing?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (Go to 93)
92	If Yes, how many times have you been admitted in the past year?	<input type="checkbox"/> 1-2 <input type="checkbox"/> 3-5 <input type="checkbox"/> 6-10 <input type="checkbox"/> >10

ALLERGY SYMPTOMS

93	Have you ever had 'hayfever'? (itchy/watery eyes and runny nose and sneezing)	<input type="checkbox"/> Yes <input type="checkbox"/> No		
94	Have you ever had eczema (or bommels)?	<input type="checkbox"/> Yes <input type="checkbox"/> No		
	Have you ever had allergies to any of the following? <i>Circle answer.</i>	Item	Yes/No/Don't Know	
		95	Dog	Y / N / DK
		96	Cat	Y / N / DK
		97	Bees	Y / N / DK
		98	Nuts	Y / N / DK
		99	Fish	Y / N / DK
		100	Grass	Y / N / DK
		101	Other	Y / N / DK
102	(specify): _____			

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Have any of your children ever had any of the following? Record for each child. *Circle answer. If no children, write "N/A" under DOB.*

		Child 1	Child 2	Child 3	Child 4	Child 5	Child 6
103	D.O.B (DD/MMM/YYYY)						
104	Gender	M / F	M / F	M / F	M / F	M / F	M / F
105	Hayfever	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK
106	Wheezing	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK
107	Eczema	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK
108	Allergies	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK
109	Asthma	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK
110	Been on medicine for asthma	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK
111	Number of visits to emergency unit or hospital for asthma in past year						
112	Tested for TB	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK	Y / N / DK

TUBERCULOSIS

113	Have you been tested for TB in the last year?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q118)
114	If Yes, were you started on treatment? + If yes, record in medication chart	<input type="checkbox"/> Yes (if yes, skip to Q116) <input type="checkbox"/> No ↓
115	If No, why not? After this question, skip to Q118.	<input type="checkbox"/> It wasn't TB <input type="checkbox"/> Didn't go back for results <input type="checkbox"/> Not able to take treatment <input type="checkbox"/> Other (specify):
116	Have you currently:	<input type="checkbox"/> Completed treatment (skip to Q118) <input type="checkbox"/> Still on treatment (skip to Q118) <input type="checkbox"/> Did not complete treatment ↓

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117	What was the reason you did not complete treatment?	<input type="checkbox"/> Unable to take medication <input type="checkbox"/> Got better <input type="checkbox"/> Unable to get to clinic for follow up <input type="checkbox"/> It was not TB <input type="checkbox"/> Other (specify): _____
118	Has anyone <i>in your household or close family</i> , including those who have died, been treated for TB in past year?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q121) <input type="checkbox"/> Don't know (if no, skip to Q121)
119	If Yes, was he/she your: <i>Tick all that apply.</i>	<input type="checkbox"/> Adult in the house <input type="checkbox"/> Child What age is the child: _____ <input type="checkbox"/> Adult visitor <input type="checkbox"/> Neighbour <input type="checkbox"/> Other (specify): _____
120	Are any of them currently being treated for TB?	<input type="checkbox"/> Yes <input type="checkbox"/> No

TOBACCO USE

121	Do you currently smoke any tobacco products, such as cigarettes, cigars or pipes?	<input type="checkbox"/> Yes (if yes, skip to Q125) <input type="checkbox"/> No ↓
122	If you do not currently smoke, have you ever smoked in the past?	<input type="checkbox"/> Yes ↓ <input type="checkbox"/> No (if no, skip to Q138)
123	If yes, how many cigarettes did you smoke on average per day?	<input type="checkbox"/> 0-5 <input type="checkbox"/> 6-10 <input type="checkbox"/> 11-20 <input type="checkbox"/> 21-30 <input type="checkbox"/> 31-40
124	If you smoked in the past, for how long did you smoke? <i>If only a past smoker, continue to Q138</i>	Number of months: _____
125	How often do you smoke tobacco products?	<input type="checkbox"/> Every day <input type="checkbox"/> A few times per week <input type="checkbox"/> A few times per month

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126	How long ago did you first start to smoke?	Number: ____ years ago		
	On average, how many of the following items do you smoke per week? <i>If none, record 0.</i>	Tobacco Product		
		127	Manufactured cigarettes	Avg #
		128	Hand rolled cigarettes	
		129	Pipes of tobacco	
		130	Cigars	
131	Hubbly Bubbly/hookah pipe			
132	How soon after waking do you smoke your first cigarette?	<input type="checkbox"/> Within 5 minutes <input type="checkbox"/> 5-30 minutes <input type="checkbox"/> 31-60 minutes		
133	Do you find it difficult to refrain from smoking in places where it is forbidden? e.g. church, library, etc.	<input type="checkbox"/> Yes <input type="checkbox"/> No		
134	Which cigarette would you hate to give up?	<input type="checkbox"/> First in the morning <input type="checkbox"/> Any other		
135	On average, how many cigarettes a day do you smoke?	<input type="checkbox"/> 10 or less <input type="checkbox"/> 11-20 <input type="checkbox"/> 21-30 <input type="checkbox"/> 31 or more		
136	Do you smoke more frequently in the morning?	<input type="checkbox"/> Yes <input type="checkbox"/> No		
137	Do you smoke even if you are sick in the bed most of the day?	<input type="checkbox"/> Yes <input type="checkbox"/> No		

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PHYSICAL EXAMINATION			
138	Weight		(kg)
139	Height		(cm)
140	Height of Fundus (SF measurement)		(cm)
141	Blood pressure		
142	Heart Rate		per minute
143	Respiratory Rate		per minute
144	Witnessed cough	<input type="checkbox"/> Yes <input type="checkbox"/> No	
145	Audible wheeze	<input type="checkbox"/> Yes <input type="checkbox"/> No	
	Record if any of the following are present: <i>Circle answer.</i>		Yes/No
		146 Clubbing	Y / N
		147 Pallor	Y / N
		148 Oedema	Y / N
		149 Jaundice	Y / N
150	Chest auscultation: Is chest auscultation normal?	<input type="checkbox"/> Yes (if yes, go to Q152) <input type="checkbox"/> No. If No, complete table below.	
	Findings <i>Circle answer.</i>	A. Left Side Yes/No	B. Right Side Yes/No
151	Wheeze	Y / N	Y / N
152	Have you been diagnosed with any of the following today? <i>Tick all that apply.</i>	<input type="checkbox"/> HIV <input type="checkbox"/> High blood pressure <input type="checkbox"/> TB <input type="checkbox"/> Diabetes <input type="checkbox"/> Pneumonia <input type="checkbox"/> Infection <input type="checkbox"/> Asthma (wheezing) <input type="checkbox"/> Other (specify): _____	
153	Was any medication started today? + <i>If yes, record in medication chart</i>	<input type="checkbox"/> ARVs <input type="checkbox"/> Supplements/multivitamins <input type="checkbox"/> Antibiotics <input type="checkbox"/> Anti-hypertensive/blood pressure meds <input type="checkbox"/> Iron <input type="checkbox"/> TB Meds <input type="checkbox"/> Other (specify): _____	

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154	<p>Were any of the following investigations done today? <i>If yes, complete on maternal results form.</i></p>	<p><input type="checkbox"/> FBC <input type="checkbox"/> Urine Dipstick <input type="checkbox"/> U & E <input type="checkbox"/> Haemoglobin <input type="checkbox"/> Random Glucose Level <input type="checkbox"/> Fasting Glucose Level <input type="checkbox"/> 24 Hour Urine Creatinine Collection <input type="checkbox"/> Urine MC&S <input type="checkbox"/> Other (specify): _____</p>
CRF Completed by: _____		Date: ____/____/____ DD / MMM / YYYY