A LONGITUDINAL STUDY OF ANTENATAL DEPRESSION AND ANXIETY IN URBAN BLACK SOUTH AFRICAN WOMEN

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A THESIS

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Declaration

I, Stephanie Elaine Redinger, declare that this thesis is my own original, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other University or institution.

Signed: 

30th day of September 2021

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Chapter 5 (In press, S. Afr. Med. J. 2021)

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Acronyms and abbreviations

APA	American Psychiatric Association
CHBAH	Chris Hani Baragwanath Academic Hospital
COVID-19	Coronavirus disease 2019
DOHaD	Developmental Origins of Health and Disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPDS	Edinburgh Postnatal Depression Scale
HIC	High income countries
HPA	Hypothalamic–pituitary–adrenal
ICD-11	The International Classification of Diseases
LMIC	Low and middle income countries
NCDs	Non-communicable diseases
RCT	Randomised control trial
S1000	Soweto First 1000 Days Cohort
SEM	Structural equation modelling
STAI	State Trait Anxiety Index
TSH	Thoughts of self-harm

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Firstly, I need to thank my supervisor and mentor, Tamsen Rochat, who has invested so much into making me the researcher I am today. Her unwavering support and encouragement have steered me through not only this thesis submission, but also over many other hurdles the last 5 years.

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I am hugely grateful to my parents, Sarah and Patrick, who fostered a love of learning about the world around me, and for giving me the gift of education. Their daily check-ins have fuelled me on the toughest of days. A big thank you too, to my in-laws, Shirleen and Werner, whose friendship and kindness are a huge blessing. I am grateful for the encouragement from my siblings, family and friends - and their grace shown towards me on this journey.

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Preface

"If we change the beginning of the story, we change the whole story."

Raffi Cavoukian, The Beginning of Life

My interest in perinatal mental health began while I was working as an Occupational Therapist for the Department of Health in a small rural hospital in KwaZulu-Natal. A lot of my clinical work involved intervening with neonates and young children with neurodevelopmental problems or other developmental delays. Through reading the literature around early childhood development, in particular research about attachment and responsive caregiving, I realised that if I wanted to learn about how to improve outcomes for children during the perinatal period and early years, I needed to focus on the caregiver first. I had always focused on the child I could see in front of me – and while I considered perinatal influcences on development such as HIV-exposure, fetal alcohol syndrome, or preterm birth -I had not given much consideration to maternal mood in the antenatal period as an influence on the fetal environment.

Through learning about the work of the Developmental Pathways for Health Research Unit (DPHRU), I was introduced to the field of lifecourse development, and the developmental origins of health and disease. These fields of medical research are interested in the perinatal environment, exposures to environmental factors, interaction between environmental and genetic factors, and how these influence health and disease risk across the lifecourse.

Through discussions with my supervisors, I realised that DPHRU was a good academic home for me, and am grateful that they afforded me the opportunity to work on the mental health dataset of the Soweto First 1000 days cohort for my Masters project. I was fortunate enough to receive a Masters scholarship through the Centre of Excellence in Human Development in 2016, which was a catalyst for me to leave clinical work and pursue a career in research. After making good progress in the Masters study (being able to publish the results in an international journal), and having an analytical plan to further investigate the S1000 antenatal mental health data, I was able to upgrade the study into a PhD in 2018.

The result is a thesis with publications included as chapters, as each answers a specific objective of the research. All three publications have been published in peer reviewed journals. The structure of the thesis is outlined as follows:

Section 1: Background and literature review

Chapter 1 provides an orientation to the key literature on antenatal depression and anxiety, presents a conceptual framework and outlines the research gaps in the current literature - both of which informed the analytical approach in the series of publications.

Chapter 2 describes in greater detail the overall methodology, including study setting, participants, data collection and management, and ethical approvals.

Section 2: Empirical Chapters

Chapters 3-5 present each of the peer reviewed publications that represent the body of the doctoral study.

1. Chapter 3: First trimester antenatal depression and anxiety: Prevalence and associated factors in an urban population in Soweto, South Africa
2. Chapter 4: Antenatal depression and anxiety across pregnancy in urban South Africa
3. Chapter 5: Thoughts of self-harm in early and late pregnancy in urban South Africa: Investigating prevalence, predictors and screening options

Part 3: Integrated Discussion and Conclusion

Chapter 6 integrates the results of the three publications, synthesising the main research findings, and outlining the methodological and clinical contributions of the work. The findings are interpreted within the context of the existing evidence base in South Africa and globally.

Chapter 7 concludes the thesis with an evaluation of the study strengths and limitations, the relevance and implications of these findings, and outlines considerations for future research.

Abstract

Introduction

Pregnancy is a time of tremendous change and adjustment for women, their partners and families. This adjustment is made more difficult when pregnancies are higher risk, unplanned, unsupported or are marred by negative life experiences. Globally, approximately one in three pregnant women experience mental health problems at some point during their pregnancies, with depression and anxiety being most common, and problems more likely to persist into the postnatal period and beyond if not addressed. Despite being relatively common, very few health care systems, especially those in lower resourced settings such as South Africa, include routine screening for and access to care for mental health problems in pregnancy.

Unidentified and untreated antenatal depression and anxiety can have a myriad of negative consequences for the affected woman, her partner, their fetus and family. This includes lower uptake and compliance with antenatal care and health behaviours, negative pregnancy outcomes and even thoughts of self-harm (TSH) that can potentially escalate to antenatal self-harming behaviours or suicide. Given growing evidence of a high burden of mental health problems amongst South African women, there is a need to address the gaps in South African literature around our understanding of how and when antenatal depression and anxiety present in pregnancy, what best predicts its onset and persistence and what health care systems can do to prevent some of the worse outcomes of antenatal mental health problems, specifically the risk of self-harm.

Aims

The overall aim of this study is to determine rates of antenatal depression and anxiety in an urban population in Soweto, South Africa, and to determine the factors associated with them using a longitudinal pregnancy cohort. It aims to better understand, in a context of high adversity, the stress and protective factors which interact with psychological vulnerability during pregnancy, in order to make recommendations for screening in clinical settings and potential intervention targets.

Methods

Women were enrolled in a prospective pregnancy cohort Soweto First 1000 Days Cohort (S1000) in Soweto, South Africa (2014–2016) and assessed using validated measures including Edinburgh Postnatal Depression Scale (EPDS) with a score of ≥13 indicating probable depression; and the State-Trait Anxiety Index (STAI) with a score ≥12 indicating probable anxiety. Data was collected in early (T1) and later pregnancy (T2) from a cohort of 1063 women (2014-2016) however longitudinal analysis in this thesis is restricted to n=649 women with mental health data at both time points. Sensitivity analysis indicated little to no difference to those included in terms of mental health and other important socio-demographic variables although those included in the n=649 had slightly higher asset ownership scores.

Logistic regression was used to determine factors associated with depression and anxiety at each timepoint, while multinominal regression modelling was used to determine factors associated with transient versus persistent depression, anxiety and TSH across pregnancy. Cross-lagged panel modelling explored direction of effect between depression, anxiety, and stressors. Lastly, bifactor confirmatory factor analysis was used to investigate the existence of a general latent factor for depression and anxiety, and what the association of this general factor was to TSH.

Results

Prevalence of antenatal depression in the first trimester was 27% (95% CI 24.2-29.8) and anxiety 15.2% (95% CI 12.9-17.5). Factors associated with antenatal depression and anxiety were predominantly relationship- and family-centred. Women who perceived that their partner made life harder for them had threefold increased odds for depression (OR 3.33 [2.28-4.85] p<0.001 while those with family stressors had almost double the odds for depression (OR 1.78 [1.22-2.59] p=0.003) and anxiety (OR 1.75 [1.44-2.69] p=0.001)

The longitudinal analysis found high rates of depression (T1: 27%; T2: 25%) and anxiety (T1: 15%; T2: 17%) across pregnancy. Pregnant women reporting ‘my partner made my life harder’ had higher risk ratios for persistent depression (RR 5.92 95% CI [3.0-11.8] p<0.001); family stress increased risk for persistent anxiety (RR 1.71 95% CI [1.1-2.7] p=0.027). We found evidence of a direct effect of early

depressive symptoms (T1) on later family stress (T2); and early family stress (T1) on later anxious symptoms (T2).

In the longitudinal analysis, 18% reported TSH at some stage during their pregnancy. Prevalence of TSH was slightly higher in early pregnancy (12.5%) than later pregnancy (11.6%). In multivariate logistic regression, TSH was associated with a history of mental illness (aOR 4.17 95% CI [1.3-13.7] p=0.020); concurrent depression (aOR 4.81 95%CI [2.7-8.6] p<0.001); marital stress (aOR 1.74 95%CI [1.0 - 3.0] p=0.040), and practical support (aOR 0.43 95%CI [0.2-1.0] p=0.040). Bifactor analysis examining depression and anxiety scales showed that the TSH item contributed the highest variance to a shared depression and anxiety factor in early pregnancy. Logistic regressions showed that early depression was a strong predictor of later reports of TSH.

Limitations

This research is limited in that it used screening measures of depression and anxiety rather than clinical interviews and the absence of a third timepoint in pregnancy prevented trajectory analysis. Limitations included that partner mental health data was not collected and although TSH was measured, no data was collected on plans, means or intent or history of suicidal behaviour.

Conclusion

This research illustrates that antenatal depression and anxiety are common in pregnancy – being reported by approximately a third of women – and that partner and family relationships are central risk and resilience factors. Concerningly, this research also finds that the risk of TSH during pregnancy is relatively common and also starts early in the pregnancy. Since practical support and a good marital relationship reduce the risk of depression, anxiety and TSH, these may be important avenues of focus for intervention design.

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SECTION 1: BACKGROUND AND LITERATURE REVIEW

Chapter 1 : Introduction

1.1 Maternal mental health: a global public health challenge

Studies in the last two decades have illustrated that the perinatal period is a time of high risk for mental health disorders (1-3). When considering the multitude of physical, hormonal and emotional changes occurring during pregnancy, this is not surprising. The Lancet Perinatal Mental Health series in 2014 (2, 4) provided further evidence for the contribution of these maternal mental health disorders to negative perinatal outcomes for both mothers and their offspring. Despite this, maternal mental health continues to remain under-researched, particularly in low- and middle-income countries (LMIC) where the burden is highest (5).

It is understandable that the focus of maternal health interventions in LMIC has primarily been on the physical health of the mother when considering the life-threatening nature of the conditions common to pregnancy and childbirth in these settings- including high blood pressure, infections, haemorrhage during and after labour, obstructed labour or unsafe abortions (6). Women living in these areas have higher rates of maternal morbidity and mortality, as evidenced by the maternal mortality ratio, which in 2015 was 239 per 100 000 live births in developing countries versus 12 per 100 000 live births in developed countries (7). Despite this, maternal mental health disorders are gaining recognition and scientific interest in these areas given their direct or indirect impact on many other maternal health outcomes.

It is widely accepted that the causal pathways for antenatal depression or anxiety are complex, and in reviewing the literature it has become clear that there are multiple potential exposures for both disorders during pregnancy. This study attempts to contribute to the evidence in LMIC specifically, to aid our understanding of how, when and why antenatal depression and anxiety occur, and what might be done to decrease their prevalence, as well as their impact on maternal and child health.

1.2 Conceptual framework

There are several theoretical approaches which have informed the understanding of the development of depression – both during pregnancy, and outside of the perinatal period. Most approaches fall into one of three categories: biological, psychological or social perspectives or a combination of these.

The conceptual framework shown in Figure 1.1 summarises the literature on risk factors for and outcomes of antenatal depression and anxiety, taking into account the evidence for biological, psychological and social exposures and pathways. The biological pathways from maternal depression and anxiety to maternal and child outcomes is based on Herba et al's model described in their review of mechanisms underlying maternal depression in LMIC (5).

Historically, depression and anxiety research and clinical management have been predominated by biological or medical approaches. Biological models view depression as a consequence of genetic vulnerability or of biological systems. While family and twin studies have demonstrated the influence of genetic vulnerability on the development of depression or anxiety, no specific genetic factor has been identified which might predispose one to these disorders. It is assumed, however, that genetic variations influence biological dysregulations associated with depression or anxiety. Studies within the field of Developmental Origins of Health and Disease (DoHAD) for example have shown that in the perinatal period (which is the period when women have the most significant endocrine changes) depression and anxiety are associated with dysregulation in the stress response system - the hypothalamic–pituitary–adrenal (HPA) axis (8). This pathway is illustrated in green in Figure 1.1.

Psychological models, such as the cognitive behavioural model, view depression during pregnancy as a result of individual psychological perspectives – considering pregnancy as a series of developmental processes influenced not only by personality, but also by present or past life events (9). Social models view pregnancy as a socially constructed experience, focusing on how the development of depression is influenced by the contextual, environmental and interpersonal factors of the individual. These models acknowledge that pregnancy is a period of adjustment in any woman's life when roles and identity shift, and when relationships often become redefined.

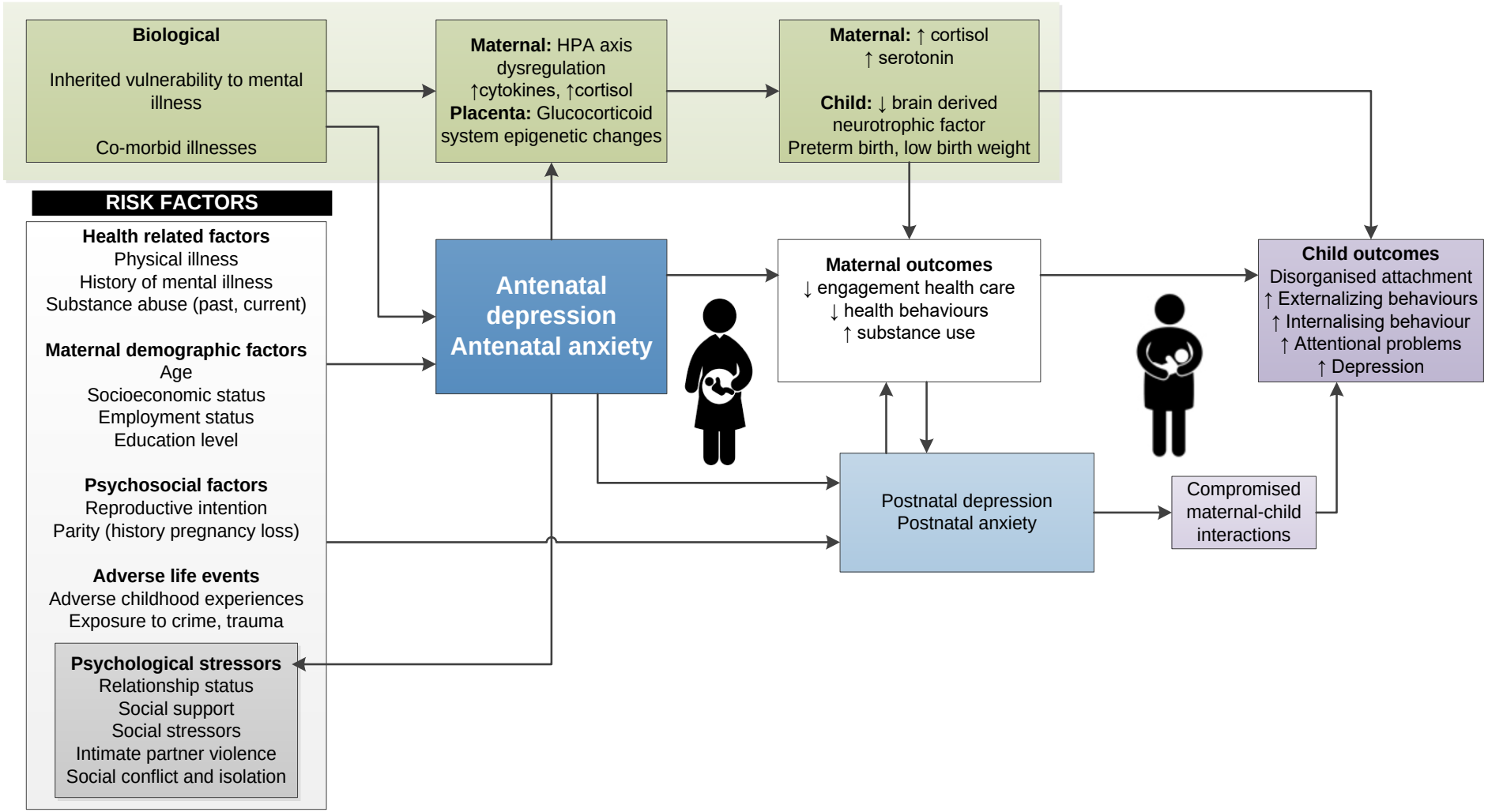

Figure 1.1 Conceptual framework of the risk factors for and impact of antenatal depression and anxiety

Given this conceptual overview of the literature, in the literature review I will outline how depression and anxiety are defined in the antenatal period, as well as describe how prevalent they are globally and in South Africa. I will also describe will describe the global and local literature on risk and protective factors for both disorders as shown in Figure 1.1, and how each these can be understood using a vulnerability-stress framework. Lastly, I will describe what is known about the impact of both disorders on later maternal and child outcomes, and the interventions which have been tested in South Africa to date.

1.3 Literature review

1.3.1 Defining antenatal depression and anxiety

There are two official categorisation systems for mental disorders – The International Classification of Diseases (ICD-11) published by the World Health Organization (WHO), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published by the American Psychiatric Association (APA). While both are seen as authoritative guidebooks for researchers and clinicians for the reporting, diagnosis and treatment of mental disorders, there are some differences in the categorisation of disorders and therefore I will consider both in defining antenatal depression and anxiety.

Antenatal depression

The DSM-V (10) and the ICD-11(11) define a depressive episode as a two week period characterised by at least five of the following symptoms: depressed mood/irritability; decreased interest in activities; significant weight or appetite changes; sleeping problems (insomnia or hypersomnia); psychomotor agitation and/or retardation; fatigue; feelings of worthlessness/guilt; inability to concentrate or think clearly; recurrent TSH and/or suicide. At least one of the first two symptoms (depressed mood/irritability; decreased interest in activities) must be present. The DSM-IV listed a criterion for depression with “postpartum onset,” which was amended in the DSM-V to “peripartum onset” in order to account for depression starting during pregnancy or up to 4 weeks postpartum. Depression occurring during pregnancy, or antenatal depression, therefore has the same criteria for diagnosis as depression in non-child bearing individuals, with the specifier indicating timing of onset of symptoms. In clinical practice and epidemiological research however, pregnancy and the first 12 months postnatal is generally considered the “perinatal” period while

“antenatal” describes the pregnancy period, and “postnatal” the period starting at birth up to 12 months postnatal.

Antenatal anxiety

While there are a number of different types of anxiety disorders, the most commonly diagnosed, including in the perinatal period, is generalised anxiety disorder. In order to be diagnosed as anxiety, symptoms must cause clinically significant distress or impairment in functioning, occur for at least six months and not be attributable to the effects of a substance, a medical condition or another mental disorder (10). Given that the field of antenatal anxiety is still relatively new, currently anxiety disorders in the DSM-V do not have a specifier for antenatal onset of anxiety or for the persistence of pre pregnancy anxiety into pregnancy.

However, definitions for generalised anxiety are useful and commonly used in pregnant populations. These definitions require that a woman must have excessive anxiety or worry that she finds difficult to control about a number of events or activities resulting in significant distress or impairment in functioning. This must be accompanied by at least three of the following symptoms occurring on most days for six months: restless or feeling keyed up or on edge, being easily fatigued, difficulty concentrating/mind going blank, irritability, muscle tension, and sleep disturbance.

Co-morbid antenatal depression and anxiety

Depression and anxiety often co-occur, within and outside of the perinatal period with many overlapping symptoms (irritability or agitation, worry, guilt, sleep problems and self-doubt) (12). The ICD-11 includes a diagnosis for “mixed anxiety and depressive disorder” which is characterised by co-occurring, subsyndromal symptoms of anxiety and depression, severe enough to justify a psychiatric diagnosis, where neither is clearly predominant (13). The overlapping presentations are believed to be driven, in part, by shared biological pathways in neurotransmitters with both featuring lower than normal serotonin, dopamine and epinephrine levels.

1.3.2 Prevalence of antenatal depression, and anxiety

Perinatal depression and anxiety are recognised as the most common complications of pregnancy and up to 12 months postpartum, with up to 25% of women globally being affected (2). Within the perinatal period, antenatal studies are less common than postnatal as seen in the most recent systematic review which found 42

antenatal studies, and 79 postnatal studies reporting prevalence of mental illness (14). In contexts where women live in high adversity, such as those living in low resourced settings, risk for perinatal mental disorders has been shown to be higher than high-income countries (HICs) (15, 16). However, estimates vary greatly across regions, population types, and depending on the diagnostic assessment or screening instruments used (14).

Alarmingly, despite Africa having one of the largest populations of pregnant women in the world (17), and authors describing rates of perinatal depression as 'epidemic' in sub-Saharan Africa (18), less than quarter of LMIC studies on both antenatal and postnatal mental health problems have been undertaken on the continent (19).

Prevalence of depression

Systematic reviews have generally estimated a greater antenatal depression prevalence's in LMICs, ranging from 19.0% to 25.3% (12, 16), compared to HIC, where prevalence ranges between 6.5% and 12.8% (1, 21). The most recent estimates antenatal depression prevalence from a meta-analysis of the global literature in 2017 is 9.2% in HIC and 19.2% in LMIC (14, 22), while a review in 2016 of LMIC only found a slightly higher prevalence of antenatal depression of 25.8%

As shown in the summary of the antenatal depression literature in South Africa to date (Table 1.1) research interest in this area has increased over the last decade resulting in fifteen publications reporting prevalence. The South African evidence base is however limited in that studies have generally measured depression but not anxiety; this despite increasing evidence that anxiety is common and associated with negative outcomes (23). Furthermore, no studies to date have focused specifically on early pregnancy (first trimester), with the vast majority of women being in their second or third trimesters, and almost all studies being cross-sectional.

Only three South African studies report specifically on women in their first trimester (24-26). Evidence to guide screening and intervention in the first trimester of pregnancy, where preventive interventions may have their biggest impact, is therefore limited. Nonetheless, these South African publications (including two diagnostic studies) confirm that mental health disorders are common in pregnancy, reporting prevalence's ranging from 11 to 48%. Research from KwaZulu-Natal and Mpumalanga consistently reports rates over 40%, however these samples were in

women with higher risk profiles, for example high rates of HIV. Gauteng, despite having the largest population of all 9 provinces in South Africa, is under researched in this area, with only 2 studies of antenatal populations in the last 10 years.

Table 1.1 Studies of the prevalence of antenatal depression in South Africa

Study reference	Province	n	Screening tool*	Trimester	Reported prevalence
Rochat et al., 2006, 2011 (27, 28)	KZN	242 109	EPDS ≥13 SCID	2nd	41% 47%
Hartley et al., 2011 (26)	WP	1062	EPDS ≥14	1st (n=63) 2nd (n=489) 3rd (n=510)	39%
Honikman et al., 2012 (29)	WP	5407	EPDS ≥13	mean 24 weeks	32%
Manikkam et al., 2012 (25)	KZN	387	EPDS ≥13	1st (n=16) 2nd (n=86) 3rd (n=226)	38.5%
Tomlinson et al., 2014 (30)	WP	1126	EPDS ≥13	mean 25.9 weeks	41%
Richter et al., 2014 (31)	KZN	1200	GHQ≥7	2nd	14.1%
Brittain et al., 2015 (32)	WP	726	BDI ≥20	2nd	21%
van Heyningen et al., 2016 (24)	WP	376	MINI	1st (n=90) 2nd (n=181) 3rd (n=105)	22%
Peltzer et al.2016 (33)	MP	663	EPDS ≥13	2nd	48.7%
Wong et al., 2017 (34)	WP	625	EPDS ≥13	1st (n=41) 2nd (n=355) 3rd (n=229)	11%
Marsay et al., 2017 (35)	GP	145	EPDS ≥13	2nd 3rd	19%
Rodriguez et al., 2018 (36)	MP	69	EPDS ≥12	mean 18 weeks	45%
Tuthill et al., 2018 (37)	KZN	68	PHQ-9>10	3rd	57%
Garman et al., 2019 (38)	WP	384	HDRS 17-item ≥17/54 MINI	3rd	40.9%

*EPDS – Edinburgh Postnatal Depression Scale; SCID – Structured Clinical Interview for DSM; GHQ – General Health Questionnaire; BDI-II – Beck Depression Inventory; MINI - Expanded Mini-International Neuropsychiatric Interview; HDRS - Hamilton Depression Rating Scale.

Prevalence of anxiety

Antenatal anxiety has been found to be relatively common in HIC and LMIC with an overall global prevalence of 15.2% (39). A 2010 systematic review of 35 studies across eight African countries found that very few studies on the continent assessed mental health problems other than depression (19), and this continues to be the norm a decade later (12). This review reported prevalence of antenatal anxiety as 14.8% - which is slightly higher than rates seen in HIC studies (15). While little research has

been done into the course of anxiety disorders in the perinatal period, what is known is that they are highly comorbid with depressive disorders (40).

As seen in Table 1.2, there is a dearth of literature on antenatal anxiety in South Africa, and also in Africa. There is also little consensus around screening tools to be used, and prevalence ranges are wide.

Table 1.2 Studies of the prevalence of antenatal anxiety in South Africa and Africa

Study reference	**Province**	**n**	**Screening tool***	**Trimester**	**Reported prevalence**
Roos et al., 2013 (41)	WP	105	STAI	2nd 3rd	Not reported
van Heyningen et al., 2017 (42)	WP	376	MINI	1st (n=90) 2nd (n=181) 3rd (n=105)	18%
Marsay et al., 2017 (35)	GP	145	EPDS-A	2nd 3rd	14.5%
Study reference	**Country**	**n**	**Screening tool***	**Trimester**	**Reported prevalence**
Adewuya et al., 2006 (43)	Nigeria	172	SCID	3rd	39.0%
Bindt et al., 2012 (44)	Ghana Cote d'Ivoire	1030	GAD-7≥10	3rd	11.4% 17.4%
Ngocho et al., 2019 (45)	Tanzania	200	BSI≥1.01	Mean 28 weeks	23.%

*STAI – Spielberger State Anxiety Index; MINI - - Expanded Mini-International Neuropsychiatric Interview; EPDS-A– Edinburgh Postnatal Depression Scale anxiety subscale; SCID – Structured Clinical Interview for DSM; GAD-7 - Generalised Anxiety Disorder Assessment.

1.3.3 Risk factors for antenatal depression and anxiety

There are multiple known risk and protective factors associated with antenatal depression (5) but there is less evidence on factors associated with anxiety in the literature. Some risk and protective factors are shared across settings while others differ slightly by context. Factors in HIC and LMIC include both individual and contextual conditions, summarised in Figure 1.2 (5, 15, 23).

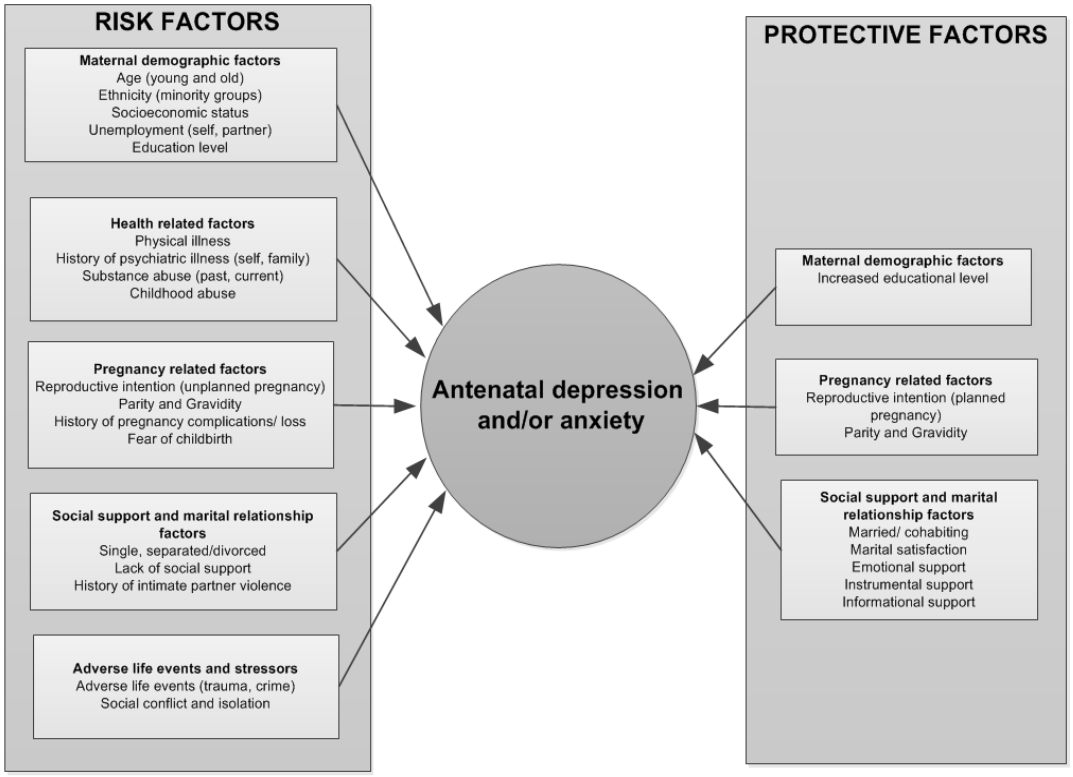

Figure 1.2 Factors associated with antenatal depression and anxiety from systematic reviews

One of the earliest systematic reviews of the perinatal mental health literature in LMICs was conducted by Fisher et al in 2012 (16). They found 13 papers on the antenatal period, however data was only available for 9 of these (representing 8% of all LMICs). This study found perinatal mental disorders were associated with socio-economic status, unplanned pregnancy, young age, being unmarried, lack of partner support, intimate partner violence, having hostile in-laws and having insufficient practical support. At a similar time, a systematic review was published on psychological wellbeing during the perinatal period in Africa specifically – finding 12 antenatal and 23 postnatal studies. Their results showed that a few studies found lack of support and relationship conflict were associated with increased odds of mental health disorders, and that the evidence of the effects of sociodemographic variables was inconclusive.

A limitation of the reporting of the risk factors in both of these systematic review was that antenatal and postnatal studies were not disaggregated, and because there were significantly more postnatal studies (40 postnatal vs 14 antenatal) the results would be heavily weighted to the postnatal period. For example, the LMIC review found that difficulties in the partner relationship were associated with maternal depression, however only 2 of the 8 individual studies were from the antenatal period

– representing about 20% of the antenatal studies in the review. Also, given that most studies were cross-sectional, these findings are only an overview of associations of common risk factors for mental health in the perinatal period, and are not an indication of causality.

A Lancet Psychiatry series in 2016 examining the epidemiology of risk factors for and mechanisms underlying risk of perinatal mental health in LMIC provides the most recent and most comprehensive systematic review of LMIC antenatal mental health to date. This review included 51 antenatal depression studies from 20 LMICs (20/112 or 18% of all LMIC) and n= 48 904 participants; with a quarter of these studies from Africa. This review found strong evidence for associations between maternal depression and childhood abuse, as well as IPV. Additionally, they showed associations with level of educational, socioeconomic status, the amount of e social support and a history of mental illness.

Some risk and protective factors are shared across settings while others differ slightly by context. In South Africa, as with other LMICs, risk factors are specifically associated with contexts of adversity, including intimate partner violence, adverse life events, low socio-economic status, substance use and health related vulnerabilities such as HIV infection (12, 19). The absence of social support, as well as stressors within partner and family relationships are consistently associated with depression, whereas there is less conclusive evidence for the association with socio-demographic and obstetric variables (12, 32).

1.3.4 How risk factors influence antenatal depression and anxiety

When considering depression and anxiety, it is well established in the literature that both depression and anxiety have genetic components – seen in the imbalance in neurotransmitters at an individual level, making an individual more vulnerable to the disorders. Schotte et al refer to this "psychobiological substrate" as what determines the vulnerability to depression. However, a genetic vulnerability does not guarantee that a person will have clinical levels of depressive or anxious symptoms. Relative to psychotic and neurodevelopmental mental disorders, it is argued that emotional disorders have a more environmentally mediated vulnerability – in fact, more than half of the underlying risk for depression and anxiety has been shown to be attributable to environmental factors (46). In other words, depression and anxiety occur as a result of an interaction between the individual and their environment, in

fact severe enough negative environments could precipitate psychological disorders in the absence of psychological or biological vulnerability.

The vulnerability-stress model of psychopathology proposes that mental disorders result from the interaction of a vulnerability (predisposition) to the disorder and the experience of stressful events. The vulnerability-stress models postulates this as an almost seesaw effect reflecting the contributions of risk and resilience factors on outcomes (Figure 1.3).

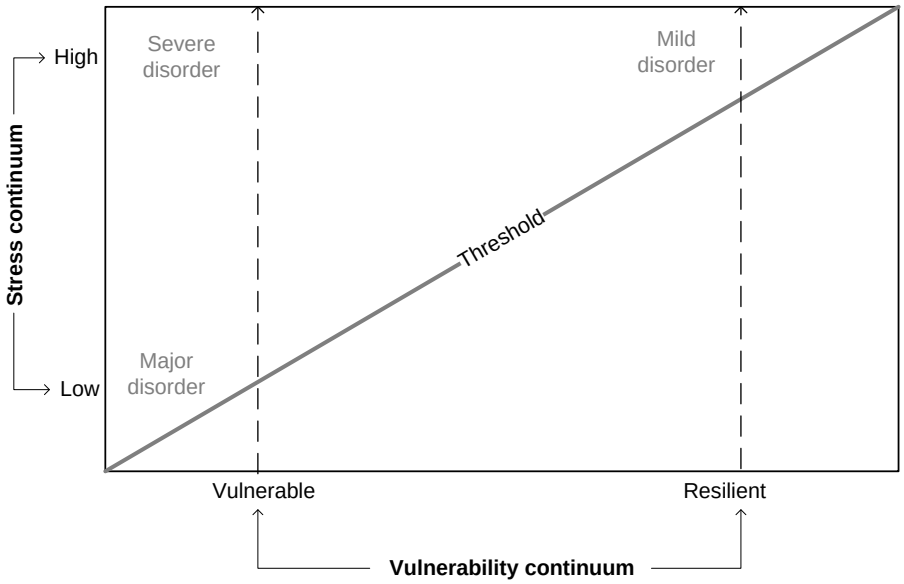

Figure 1.3 The vulnerability-stress model

This vulnerability-stress model builds on the concept that stressors act in common ways but are experienced differently by different individuals. For example, a negative life event such as a divorce may be experienced as a relief for a women in an abusive relationship whereas it can be highly distressing for a women affected by infidelity. Equally in contexts where cumulative negative events are common (e.g. poverty, illness) outcomes are more than the sum of negative experiences, instead they are the sum of negative experiences in the context of a set of buffering protective factors. As an illustration of this, COVID-19 would bring a large and significant shared environmental stressor to pregnant women, which could be worsened by concurrent poverty or illness. However, despite this shared negative stress many women (even poor women) will have individual resilience drawn from their personal relationships and social or practical supports which may mediate the effect of COVID-19 on their pregnancy experience and mental health. The vulnerability-stress framework is thus a helpful theoretical approach from which to understanding how the effects of negative environmental factors (which are shared

and often difficult to change) can be mitigated by potentially protective factors. Protective factors which are modifiable and can therefore be encouraged or increased through intervention then become productive pathways for targeted interventions in adverse settings.

In some highly adverse regions, pregnancy and childbirth can lead to life threatening experiences given disease exposures and poor access to services. In South Africa, where the context is not as dire as other regions, women still face multiple adversities - they live in low income households, have poor access to services, and 30% of the population are living with HIV or at least one other NCD (47, 48)– making pregnancy a stressful period. In this thesis, risk and protective factors will be discussed and analysed through the lens of the stress-vulnerability model. Analytic models will account for the fact that in South Africa, women are exposed to multiple simultaneous stressors, which we know can result in higher rates of the mental disorders.

1.3.5 Impact of antenatal depression and anxiety

Unidentified and untreated antenatal depression and anxiety can have a myriad of negative consequences for the affected woman, her child and their family. This includes self-harming thoughts during the pregnancy which are the precursor to self-harming behaviours or suicide. There is evidence from HIC that chronicity and persistence of mood disorders in the perinatal period has an impact on longer term outcomes for the mother and her offspring.

Impact on maternal health

A recent Lancet series of perinatal mental health provides evidence that addressing depression and anxiety as early as possible in pregnancy is important because it is detrimental to a woman's health (2). For example, internationally antenatal depression and anxiety have been found to be associated with increased substance and tobacco use in pregnancy, lower compliance with antenatal care, and decreased frequency of health behaviours such as handwashing (23, 49, 50) and in some West African studies antenatal depression has been associated with poor compliance to HIV treatment and preventive care (51). Antenatal depression and anxiety are also positively associated with postnatal depression, and are one of the strongest predictors of mental health disorders in the postnatal period (52).

Impact on suicidality

One of the most concerning associations of both disorders is with of suicide attempts, suicidal ideation, self-harm behaviours and TSH. A recent systematic review of self-harm in young people in sub-Saharan Africa found seventy-four studies from 18 countries, with South Africa contributing the most studies (53). It showed that women of child-bearing age (and adolescent girls) are at high risk for self-harm. This review re-iterated findings from the global literature that reporting of suicide attempts, suicidal ideation, self-harm behaviours and TSH is made difficult because the definitions of these terms and concepts is not consistent.

Prevalence of perinatal TSH in the global literature ranges from 5 to 18%, and is more common in LMIC (54). Risks factors for both TSH and suicidal ideation during this period include antenatal depression, anxiety, psychosocial stress (54, 55). The limited data of suicidality during pregnancy in population-based samples does make it difficult to determine whether rates are higher in pregnancy versus in age-matched non-pregnant women.

Despite high rates of perinatal mood disorders in South Africa, and the significant public health consequences of suicidality in terms of maternal morbidity and mortality, we know comparatively little about TSH in pregnant women in South Africa, and current rates vary considerably by geographical region. A study in rural KwaZulu-Natal in a sample with high rates of HIV found a prevalence of suicidal ideation of 27.5% using the Structured Clinical Interview for DSM Disorders (SCID) (56). Two studies from the Western Province using the suicidality module of the Mini International Neuropsychiatric Interview (MINI), one in Khayelitsha and the other in Hanover Park (both highly impoverished peri-urban suburbs) found a prevalence's of suicidal ideation of 7.6% and 12% respectively (57, 58). In addition to depression and anxiety, risk factors for antenatal suicidal ideation in South Africa included socioeconomic status, food insecurity, unemployment, HIV and hazardous drinking.

Impact on the fetus

In the last decade, research within the field of the Developmental Origins of Health and Disease (DOHaD) has shown that the environment in which the embryo, fetus and young child grow and develop influences not only life course health and wellbeing but also the risk of later non-communicable diseases (NCDs). While the

effect of maternal depression on the fetus is beyond the scope of this PhD, it underlies the need for early screening and intervention. It is hypothesised that during pregnancy, maternal depression can affect offspring through 3 pathways: 1) altered placental function, 2) epigenetic changes in the child, and 3) stress reactivity (12).

Impact on birth outcomes

Besides the established negative impact of antenatal depression and anxiety on maternal health, the international literature also suggests that both are associated with negative birth outcomes. A recent systematic review found associations between antenatal depression and premature delivery, and a decrease in breastfeeding initiation in HIC (50). Evidence on the impact of antenatal anxiety is scarce globally, and as a result of the relatively small evidence base findings are somewhat inconsistent (4, 23). A meta-analysis in 2014 showed slight associations with both preterm birth and low birth weight (23). When performing subgroup analysis, the same meta-analysis found that in LMIC antenatal anxiety was associated with increased risk of low birth weight.

Impact on child outcomes

There is research which shows that antenatal depression is associated with negative outcomes later in the child's life (4). Most antenatal studies to date have focused on the impact of depression on child emotional and behavioural difficulties, finding associations between antenatal depression and negative child affectivity, disorganised attachment and externalising behaviours in younger children; and externalising behaviours and increased risk of depression in older children (4). Poorer cognitive outcomes have also been shown to be associated with antenatal depression in the literature but findings are inconsistent. Longitudinal research on anxiety and child developmental outcomes is more limited, however studies have shown associations between antenatal anxiety and increased internalising and attentional problems at age 3 (59). Depression during pregnancy predicts depression during the postnatal, which perpetuates the effect on child development through altered mother-child interactions, and changes in sociodemographic or environmental contexts and social support. In longitudinal studies of depression during both the antenatal and postnatal period, timing and chronicity have been shown to be moderators of the effect of maternal depression on child developmental outcomes (60-62).

The fact that maternal mental disorders during pregnancy affect not only the mother's future health outcomes, but also has an effect on later offspring highlights the importance of understanding the factors leading to the mental disorder in the first instance. An understanding of how and when antenatal depression and anxiety present in pregnancy, what best predicts their onset and persistence can therefore inform mitigation strategies for both antenatal and postnatal mental health, and some of these outcomes described above.

1.3.6 Maternal health care in South Africa

In many healthcare systems, including in South Africa, the antenatal period is a time of increased contact with healthcare providers, making it an opportune time for monitoring of mental health symptoms. Maternal health care services during pregnancy is also one of the pillars of safe motherhood in South Africa, and therefore remains a population health priority in South Africa (63). In fact, South Africa is among the few sub-Saharan African countries to have made significant improvements with regard to maternal health and reducing rates of morbidity and mortality in the last two decades. As a component of maternal health, there is a need to focus on maternal mental health during the pregnancy period given the evidence of multiple negative consequences these cause for mothers and children.

The World Health Organization defines maternal mental health as 'a state of well-being in which a mother realises her own abilities, can cope with the normal stresses of life, can work productively and fruitfully and is able to contribute to her community' (64). Emotional mental health disorders such as depression and anxiety are strongly mediated by environmental vulnerabilities and can therefore often be successfully improved by interventions related to modifiable factors such as environmental risk, social support or even cognitive neuroscience (65), as opposed to methods focused on neurochemistry as in neurodevelopmental and psychotic disorders. Of course, there are those women with severe psychological illness (2) requiring pharmacological treatment.

In the past decade, task-shifting of mental health care services to trained lay health care workers (particularly psychosocial interventions) has been strongly advocated for in an effort to increase treatment coverage for mental health disorders in LMICs (66).

1.3.7 Research gaps

Depression and anxiety in the antenatal period remain largely under-researched in pregnancy, especially in Africa and are of public health concern because they have negative consequences for women and their offspring. Contexts with high adversity including poverty, violence, disease burden, low social and emotional support and poor access to treatment, place pregnant women at increased mental health risk. Despite this, there is a dearth of longitudinal research in lower resource settings where prevalence is often high and resources lowest.

Research on mental health in the perinatal period in South Africa has increased substantially in the past decade, however, several research gaps remain:

Firstly, most studies have focused on antenatal or to a larger extent postnatal depression, while almost none have measured anxiety in the perinatal period. *As a result, little research has elucidated the similarities, differences and interaction between depression and anxiety in pregnancy*.

Secondly, longitudinal repeated measures research remains scarce, and where longitudinal data is collected it seldom includes measures taken early in pregnancy where prevention opportunities are largest. *As a result, little is known about the pathways by which these problems emerge or persist in pregnancy or how to prevent them.*

Thirdly, despite well-documented evidence of their influence on both pregnancy and mental health few studies have interrogated partner or family support in detail or in relationship to each other in quantitative studies. Those that do seldom go beyond measuring the presence or absence of practical supports, or the exposure to extreme negative events such as gender-based violence. *As a result, the evidence on partner and family support is relatively siloed, negatively framed and provides limited insights for intervention design.*

Lastly, one of the most concerning negative outcomes of any mental health problem is the risk of potential suicide. Both depression and anxiety are known to increase TSH which is an important early warning signal of life-threatening levels of mental distress. While public perception may be that perinatal women are less vulnerable to risk of suicide – internationally suicide is one of the leading causes of perinatal mortality. Evidence is limited in South Africa but existing studies have begun to

illustrate that TSH may be high amongst perinatal women (12-39%) although most studies have been cross-sectional and largely focused on depressive syndromes. *As a result, little is known about TSH in pregnancy in South Africa settings, when or how they may emerge and potentially link to either depression or anxiety or both which limits our understanding of how to approach routine screening in public health settings.*

This thesis addresses these gaps in the literature by examining the prevalence of first and second trimester antenatal depression, anxiety and rates of TSH across pregnancy in a cohort of South African women. The research reported on in this thesis explores the associated risk and protective factors involved in onset and persistence of these mental disorders, as well as the relationship between TSH, depression and/or anxiety.

1.4 Aims and objectives

The overall aim of this study is to examine antenatal depression and anxiety and the factors associated with them, in an urban population in Soweto, South Africa. The research investigates the incidence of depression and anxiety and explores the relationship between them across pregnancy using longitudinal data. It aims to better understand, in a context of high adversity, the stress and protective factors which interact with psychological vulnerability during pregnancy, with the view to making recommendations for screening in clinical settings.

Specifically, this study aims to investigate three hypotheses:

1. That both depression and anxiety will be common in pregnancy, and are likely to be co-morbid and start earlier in pregnancy than previously reported.
2. That family, partner and relationship variables will play an important role in coping with pregnancy in a high adversity setting.
3. That in the presence of either depression or anxiety, the risk for thoughts of self-harm and threat of suicide ideation will also be high.

These hypotheses will be investigated through the following objectives.

Objective 1: To determine the prevalence of and factors associated with depression and anxiety in early pregnancy.

- What is the prevalence of antenatal depression and anxiety in early pregnancy?
- What stress or protective factors are associated with depression and anxiety in early pregnancy?

Objective 2: Develop a better understanding of the prevalence, onset and progression of both depression and anxiety in pregnancy and the factors involved in their emergence or persistence across pregnancy.

- To what extent do early depression and anxiety persist across pregnancy and what additional burden might incidence of new depression and anxiety bring to later pregnancy?
- What stress or protective factors are involved in persistence of early depression and anxiety later in pregnancy or incidence later in pregnancy?

Objective 3: To determine the extent to which women report thoughts of self-harm during pregnancy, and how this relates to depression, anxiety and other stress and protective factors.

- What is the prevalence of thoughts of self-harm during early and later pregnancy?
- What stress or protective factors are associated with thoughts of self-harm in pregnancy?
- What is the relationship between symptoms of depression, symptoms of anxiety and thoughts self-harm across pregnancy?

Chapter 2 : Methodology

This chapter provides an overview of the demographic, social, economic and health care context of the research population - Soweto, South Africa. While specific methods are discussed in Chapters 3-5, this section gives an informative overview of the research population, and provides additional detail on some of the models used for data analysis.

2.1 Study setting

2.1.1 Soweto

Soweto is an urban residential area within the City of Johannesburg Metropolitan Municipality, in the province of Gauteng, South Africa (Figure 2.1). With a population estimated at 1,6 million (40% of the population of Johannesburg) and 6357 persons per square kilometre in 2020 it is South Africa's most densely populated residential area. Soweto was established as an informal settlement for black South Africans and migrant workers during the Apartheid regime, and is a historically low socioeconomic area. The population is mostly (98.5%) Black South Africans - with Zulu, Tswana and Tsonga being the main ethnic groups.

Figure 2.1 Map showing location of Soweto within South Africa

Due to the nature of its inception, and its subsequent rapid growth, Soweto is one of the most population dense areas in South Africa and problems such as poor housing, overcrowding, high unemployment and poor infrastructure are common (Figure 2.2). Despite the rapid economic growth being seen in Soweto currently, the mean

household income is R31 968 (approx. USD 2200) per annum (67). Only 84,2% of the population live in formal dwellings, and only 55% have piped water inside their homes. Pregnant women in this population are therefore exposed to common challenges of poor housing and infrastructure, food insecurity and high non-communicable disease risk.

The rapid urbanisation phenomenon seen in Soweto has resulted in high rates of non-communicable disease including diabetes, high blood pressure and high blood cholesterol (68). Mental disorders often coexist with other non-communicable diseases and they share many risk factors.

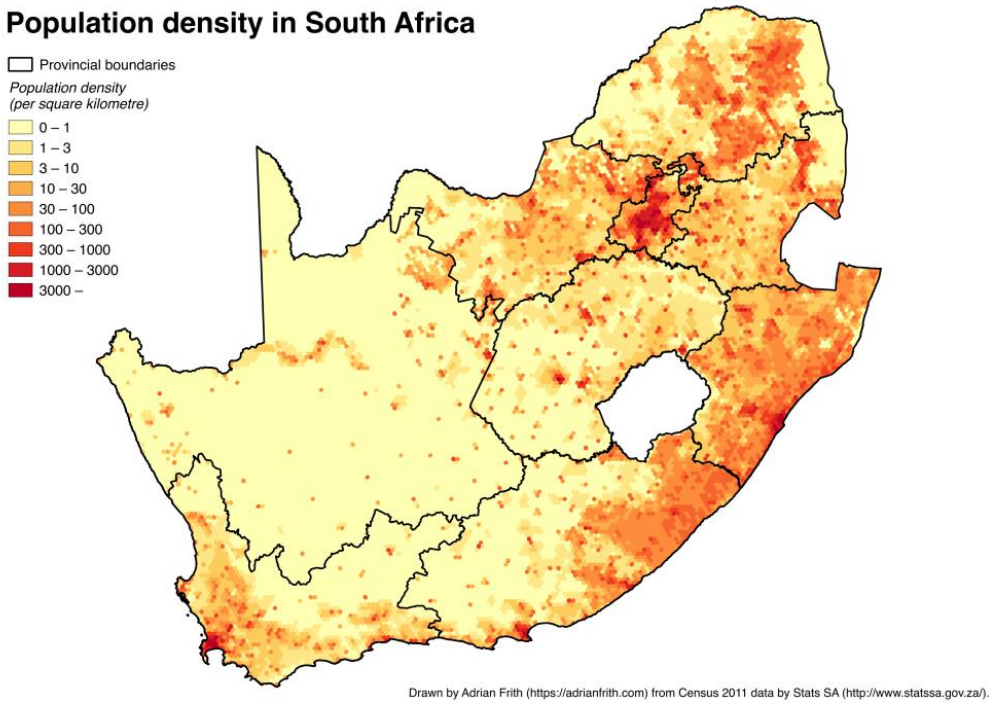

Figure 2.2 Map showing population density of South Africa

2.1.2 Healthcare in South Africa

South Africa's Constitution guarantees every citizen access to health services (section 27 of the Bill of Rights). The majority of South Africans, an estimated 84%, access health care through government funded facilities, under the National Department of Health. In South Africa, public healthcare is provided in a decentralised format, with primary health care centres and clinics at a community level referring to district level and thereafter regional or tertiary hospitals which have more specialised services (69).

2.1.3 Antenatal healthcare utilisation in South Africa

South Africa In 2020, Stastistics South Africa published The Maternal Health Indicators Report (Report no. 03-06-03) (63) which is based on healthcare indicators from the 1998 and 2016 South Africa Demographic and Health Survey. According to this report, only 47% of women had an antenatal care (ANC) visit in the first trimester, while 76% of women attended four or more ANC visits. While this is higher than most other countries on the continent (6), it is lower than rates in some other LMIC , and is concerning given that utilisation of maternal health care services has been shown in the literature to improve outcomes for both the mother and the infant during pregnancy, childbirth and during the postnatal period.

2.2 Study design and participants

2.2.1 The Soweto First 1000 Days cohort

This PhD was nested within the Soweto First 1000 days cohort (S1000) conducted by the South African Medical Research Council SAMRC)/University of the Witwatersrand (Wits) Developmental Pathways for Health Research Unit (DPHRU).

The overall aim of S1000 was to understand associations between maternal health, foetal growth and infant outcomes using repeated measures. Data collection for S1000 took place at six time points during pregnancy (<14 weeks; 14–18 weeks; 19–23 weeks; 24–28 weeks; 29–33 weeks and 34–38 weeks) and eight time points after delivery. Psychological data was collected at two timepoints during pregnancy: at 14–18 weeks (baseline) and at 24–28 weeks - here after labelled timepoint one (T1) and timepoint two (T2), respectively.

2.2.2 Chris Hani Baragwanath Academic Hospital

The Chris Hani Baragwanath Academic Hospital (CHBAH) is a tertiary-level public academic hospital located in Soweto, and serves as the highest level referral facility for a catchment area of approximately 3 million people. It is the largest hospital in Africa, and the third largest in the world. The hospital's maternity department sees 60 000 patients annually, with approximately 24 000 births. Women seen in the Fetal Medicine Unit comprise a mix of clinical risk categories, and are referred there from other primary healthcare centres when requiring fetal ultrasounds.

The Fetal Medicine Unit at CHBAH was chosen as the recruitment site for the S1000 cohort because it is the only hospital in the health district offering fetal ultrasounds –

a requirement for accurate gestational aging at recruitment, and central to the fetal growth component of the S1000 cohort.

2.2.3 Inclusion and exclusion criteria

Inclusion criteria for S1000 were as follows: resident of Soweto, or the greater Soweto area, <20 weeks pregnant, no known diagnosis of epilepsy or diabetes at the time of recruitment, 18 years or older, and a naturally conceived singleton pregnancy.

2.3 Data collection

Women were assessed at DPHRU, which is within walking distance of the antenatal clinic at CHBAH. Data collectors were trained research assistants with several years experience working with cohort participants. All participants were assessed in English or their home language when required. Psychological measures were completed using an interviewer method, with responses recorded on paper forms, and thereafter entered into an electronic dataset by data entry staff.

Data collection sheets and questionnaires for PhD specific data collection are included in Appendix A. Detailed descriptions of the data collection tools for the variables used in this PhD are provided in the individual empirical chapters to follow (Chapters 3-5).

2.4 Data management

All S1000 data was electronically captured onto the Research Electronic Data Capture (REDCap) data management platform (70), hosted by the University of the Witwatersrand. This data is stored on a secure server at the DPHRU research facility with all information and files kept in locked premises. The data manager at the research facility is the gatekeeper and requests for access and usage of the data were submitted in accordance with research unit processes.

2.5 Data analysis

While the details of data analysis are outlined in the empirical chapters, here I give a brief description of the data analytic techniques chosen and used in each publication.

Publication 1: This cross-sectional analysis was focused on determining rates of depression and anxiety in early pregnancy, and understanding what potential risk factors were associated with both using logistic regression analysis.

Logistic regressions are used to determine if an independent variable has an effect on a dependent variable, and the resultant coefficients can be used to determine odds-ratios. Multivariate logistic regression models were used in this analysis to investigate the association of several independent variables (risk factors) on the dependent or outcome variable (depression or anxiety) while accounting for the concurrent association of other variables in the model. I was therefore able to calculate what the odds were of a risk factor being independently associated with depression or anxiety, in the context of all other risk factors.

Publication 2: In this study the aim was to understand the patterns of risk emergence and duration across pregnancy, and the factors associated with transient or persistent cases of depression and anxiety using longitudinal data and multinomial logistic regression. I also investigated the causal pathways between psychological and social factors using cross-lagged panel modelling.

Multinomial logistic regression is a type of logistic regression where the outcome variable is nominal with more than two levels. This type of regression was specifically chosen for this analysis as it allowed me to determine the association of risk factors with an outcome variable which categorised women by timing or onset of depression and/or anxiety across pregnancy.

The cross-lagged panel model is a type of discrete time structural equation model used to analyse data in which two or more variables are repeatedly measured at two or more different time points. This model was used to estimate the directional effects between early depression or anxiety and later stressors (and vice versa).

Publication 3: The aim of this study was to determine rates of TSH, and their association with antenatal depression, anxiety and other factors across pregnancy, using longitudinal data and multinominal regression. Secondly, to investigate the relationship between TSH, depression and anxiety using bifactor confirmatory factor analysis.

Bifactor models are type of structural equation modelling (SEM) introduced in the literature more than 80 years (71), but only in the last decade have been proposed as an alternative to traditional factor analysis techniques for analysing the properties of psychometric scales (72). In this study bifactor confirmatory factor analysis was used

to investigate the existence of a general latent factor for depression and anxiety, and what the association of this general factor was to TSH.

2.6 Ethical approval

All women were provided with information and consent sheets prior to their inclusion in the S1000 cohort (Soweto Fetal Growth Study) Where necessary a trained member of research staff explained these documents to them in their home language. Written informed consent was then provided by all women prior to enrolment in each study component. All questionnaires were coded to ensure that participant names were not used and confidentiality was maintained. A document containing the coding links was kept separately by the Principal Investigator of SFGS. Ethical approval was obtained from the University of the Witwatersrand's Research Ethics Committee (Medical) for the S1000 study (M120524) (Appendix B) as well as for this PhD (M160670 and M180949) (Appendix C and D)

SECTION 2: EMPIRICAL CHAPTERS

Chapter 3 : First trimester antenatal depression and anxiety: Prevalence and associated factors in an urban population in Soweto, South Africa[1]

[1] Redinger, S., Norris, S. A., Pearson, R. M., Richter, L., & Rochat, T. (2018). First trimester antenatal depression and anxiety: prevalence and associated factors in an urban population in Soweto, South Africa. *Journal of Developmental Origins of Health and Disease, 9*(1), 30-40. doi:10.1017/S204017441700071X

3.1 Introduction

Antenatal depression and anxiety, the prenatal environment and child development

The prenatal environment, including maternal mental health, is increasingly recognised as having an important influence on foetal development and later offspring outcomes (4, 5, 73). Maternal mental health can lead to adverse child outcomes through altered placental function, epigenetic changes in the foetus, and stress reactivity. Depression and anxiety are the most common mental health disorders in pregnancy (1, 2) and while they may present independently, they are often co-morbid (15). Research has historically focused on postnatal depression, while more recent studies are finding prevalence rates of antenatal depression to be similar, if not higher, than postnatal depression (1). A growing body of literature finds antenatal depression and anxiety associated with poor uptake of antenatal care, increased maternal tobacco and alcohol use, as well as adverse foetal, birth and child outcomes (4, 23, 49, 50). Antenatal depression and anxiety symptoms can also increase risk of postnatal depression (52), which in turn is associated with poor maternal and child outcomes (1). As a result, antenatal depression and anxiety are an important public health research priority in both High Income Countries (HIC) and in Low and Middle Income Country (LMIC).

In the African region poverty, structural violence and threat of disease is already high (74) and the additional burden of antenatal depression and anxiety may worsen outcomes (12). Effective and timely interventions have the potential to mitigate these effects on mother and foetus with significant benefits for children, families and society (75, 76).

Prevalence of antenatal depression and anxiety in HIC versus LMIC

In high income countries (HIC) depression and anxiety affect between 7% and 20% of pregnant mothers (1, 2). As reported in two recent systematic review (12, 16), each using slightly different selection criteria, studies in LMIC have consistently reported higher rates of both depression and anxiety in pregnancy. The Bennett et al review grouped antenatal depression and anxiety as perinatal mental disorders reporting a prevalence of 15.6% (1) while the Howard et al review reported a prevalence for antenatal depression specifically as 25.3% (2). Reported risks factors in LMIC include domestic violence, negative life events, low socio-economic status (SES), absence of social support, unplanned pregnancy, prior history of mental

illness, anxiety during pregnancy and being younger in age (12, 19). It has also been shown that low support and marital/family conflict are associated with both antenatal depression and antenatal anxiety, while evidence for factors such as socio-demographic (age, education) and obstetric variables are less conclusive (12, 19).

Antenatal depression and antenatal anxiety on the African continent

The majority of research in LMICs has emanated from Asia and South America, with less than a quarter of all LMIC perinatal mental health studies being undertaken on the African continent. A systematic review of perinatal mood disorders in the African region in 2010 found only 35 antenatal and postnatal studies across eight of the 54 African countries. Only a handful of these (n=11) focused on the antenatal period, at least half of which had been undertaken between 1972-1998 (19). The review found a mean prevalence of 11.3% for antenatal depression and 18.3% for postnatal depression. Similar mean prevalence was reported for antenatal (14.8%) and postnatal anxiety (14%) based on two available studies, both from Nigeria.

In South Africa there have been several studies measuring antenatal depression in recent years which are not featured in these reviews. Almost all have focused on the third trimester of pregnancy, some have focused on antenatal depression in special populations (e.g. HIV-infected women), but none have examined antenatal anxiety. The prevalence of antenatal depression in these studies is between 21% and 41% (24-26, 28, 32). There are no studies which have looked specifically at the first trimester of pregnancy, at least in the last 5 years. It is important to look at current estimates because of evidence that rates of depression are rising (77).

There is a dearth of data from Africa and an urgent need for studies which document both depression and anxiety in pregnancy, measuring these from earliest stages of pregnancy could enhance intervention and prevention efforts. The aim of this research is to investigate the prevalence of, and factors associated with, first trimester depression and anxiety in an under-researched population of African women in an urban setting in South Africa.

3.2 Methods

3.2.1 Recruitment

The analysis reports on baseline data collected from the Soweto First 1000 Days Cohort (S1000), a prospective pregnancy cohort of women residing in Soweto, South Africa. Soweto is the most populous urban residential area in South Africa, established under Apartheid and is predominantly Black African. The S1000 cohort is a prospective sample recruited from the Fetal Medicine Unit (FMU) at Chris Hani Baragwanath Academic Hospital (CHBAH). CHBAH is a tertiary care centre, the largest hospital in Africa, with approximately 24,000 deliveries annually. A consecutive series of pregnant women attending CHBAH antenatal clinic (June 2014-July 2016) were screened to establish potential eligibility for S1000. To be included in the cohort, women were required to be: Black, residents of Soweto, ≥18 years of age, ≤ 14 weeks pregnant, and carrying a singleton pregnancy. Exclusion criteria included foetal abnormalities, major maternal physical disabilities or maternal conditions such as Type 1 diabetes and epilepsy.

3.2.2 Data collection

Enrolled pregnant women were assessed at the Developmental Pathways for Health Research Unit (DPHRU), within walking distance of the antenatal clinic. Trained research assistants with several year's experience in data collection, including working with cohort participants, collected data. All mothers were assessed in a separate private room in English or their home language when required, and the depression and anxiety measures were completed using an interviewer method. Responses were recorded on paper forms and entered into an electronic dataset by data entry staff.

3.2.3 Measurements

The four measures used in this analysis include two commonly used psychological scales, one for depression and one for anxiety. The depression scale, The Edinburgh Postnatal Depression Scale (EPDS) has been used previously in South African and African perinatal populations, and has been found to be a reliable measure with good sensitivity and specificity in local populations (78-81). It is a brief 10-item psychometric scale, which was developed to be used by primary health care professionals to screen for depression in the postnatal period but has been shown to be accurate in detecting both antenatal and postnatal depression in LMICs, including South Africa (79). The measure is scored on a severity scale (0-3) which is totalled

for a maximum score of 30. The internationally recognised threshold score for probable depression of ≥13 was used in this analysis (78, 80). The EPDS showed good internal reliability in this analysis (Cronbach's alpha 0.80). The anxiety measure was a six-item version of the state subscale of the State-Trait Anxiety Inventory (STAI), which has been constructed and validated for use in pregnant populations, and has shown high reliability (Cronbach's alpha 0.82) with the original scale (82). The measure assesses the presence of state anxiety symptoms using a Likert scale (1-4), and a summed scored is calculated. For this analysis, Cronbach's alpha was 0.64.

These two scales were supplemented by two study-specific questionnaires to measure social support and recent (previous 6 months) social stressors experienced by mothers (including relationship, family, economic and societal stressors), which were developed in previous cohort work at DPHRU and are considered reliable measures of social support and stress (83).

Social support was measured using a series of nine questions to identify the absence or presence of instrumental and emotional support, including: people available to help, a confidante, being able to speak to her partner, belonging to a community organisation/ church and having a friend with a baby. Items were used individually in the analysis. Social stress was measured using a series of sixteen questions based on common stressors, and a yes/no response indicated either the presence or absence of a stressor in the 6 months prior to the interview (prenatal and antenatal). In previous work, it was found that 10 particular stressors had a direct impact on mothers (83, 84). These stressors were grouped into 4 categories as follows: relationship stress (partner violence or relationship break-up); family stress (having a fight with/being alienated from family, having a family member with a substance abuse problem, having a disabled family member); economic stress (being in debt, having too little money for basics, having to support family members in financial need) and societal stress (being in danger of being killed, witnessing a violent crime). Cronbach alpha for this analysis was 0.54.

A wide range of socio-demographic, socio-economic and medical data was collected on the S1000 cohort. Findings from systematic reviews on factors associated with depression or anxiety in pregnancy informed a theoretical model which guided the

selection of socio-demographic, socio-economic and health related variables to be tested in this analysis (2, 12, 16, 19, 23).

These included:

Demographic status*:* Maternal age, level of education, household composition and marital status.

Socio-economics status: Socio-economic status (SES) was assessed by an asset index derived from Demographic and Health Surveys (DHS) (85). The asset score was made up of items owned by the household (electricity, radio, television, refrigerator, cell phone, personal computer, farm animals, agricultural land, bicycle, motorcycle/scooter and vehicle). The total score is used as a continuous variable in the analyses, higher scores represent higher SES.

Health: Over and above the detailed measurement of depression, anxiety, social stressors and supports, data on maternal health also included parity, reproductive intent (planned or unplanned), smoking and alcohol use in pregnancy, history of mental illness and HIV (self-report and treatment confirmation from clinic card).

3.2.4 Data cleaning and imputation

In line with guidance for the imputation of psychometric data, individual missing items on the depression and anxiety scales were imputed using the individual participant's available item series mean, derived from non-missing items for that individual on the scale. A total of 20 (2%) individual scale items were imputed (13 items on depression scale; 7 items on anxiety scale) across all participants. If a participant was missing more than 20% of the individual items on either the depression (n=9) or the anxiety scale (n=1), data was not imputed; instead the entire scale was treated as missing for that participant. No imputation was undertaken for non-scale questionnaire data.

3.2.5 Ethics

The Human Ethics Research Committee of the University of the Witwatersrand approved the study (M120524) and all participants provided written consent.

3.2.6 Data Analysis

Statistical analyses were conducted using STATA version 13 (86). Descriptive analysis was used to examine sample characteristics; sensitivity analysis used t-tests and Wilcox rank sum tests. Depression 'cases' were determined as present (1) or

absent (0) using the internationally recommended cut-off ≥13 on the EPDS (28, 78). Anxiety 'cases' were determined as present (1) or absent (0) using a cut-off of ≥12/24. This cut off score was calculated using the same cut-off ratio as the original STAI, >40/80 (87). Using these dichotomous variables for cases of depression and anxiety, univariate analysis was performed to examine associations between depression and anxiety and the women's socio-demographic, socio-economic, pregnancy and health characteristics, social support and stress variables. Thereafter we tested multivariable models using depression (model 1) and anxiety (model 2) as outcomes controlling for all variables in order to account for residual confounding.

3.3 Results

3.3.1 Sample characteristics

As illustrated in the consort diagram (Figure 3.1) 1070 women were enrolled in the S1000 cohort, of whom 946 women had completed some or all of the mental health and social support questionnaires, while 124 (12%) had missing data (16 missing all data; 108 missing both mental health measures). Statistical analysis found no evidence for significant differences when comparing those with and without missing mental health data with regards to maternal age, education, SES, marital status, parity and reproductive intention. The final analytic sample (n=946) includes women who had either one or both mental health measures, all of whom were included in univariate associations. This provides the best estimate with all available data for each individual association. However, a complete case sample across all covariates of 800 for depression data and 802 for anxiety data was used in multivariate models. Additionally, we ran univariate analysis on this complete case sample to ensure that differences between the univariate and the multivariate associations were not due to the reduced numbers (i.e., reducing from 946 to 800 or 802).

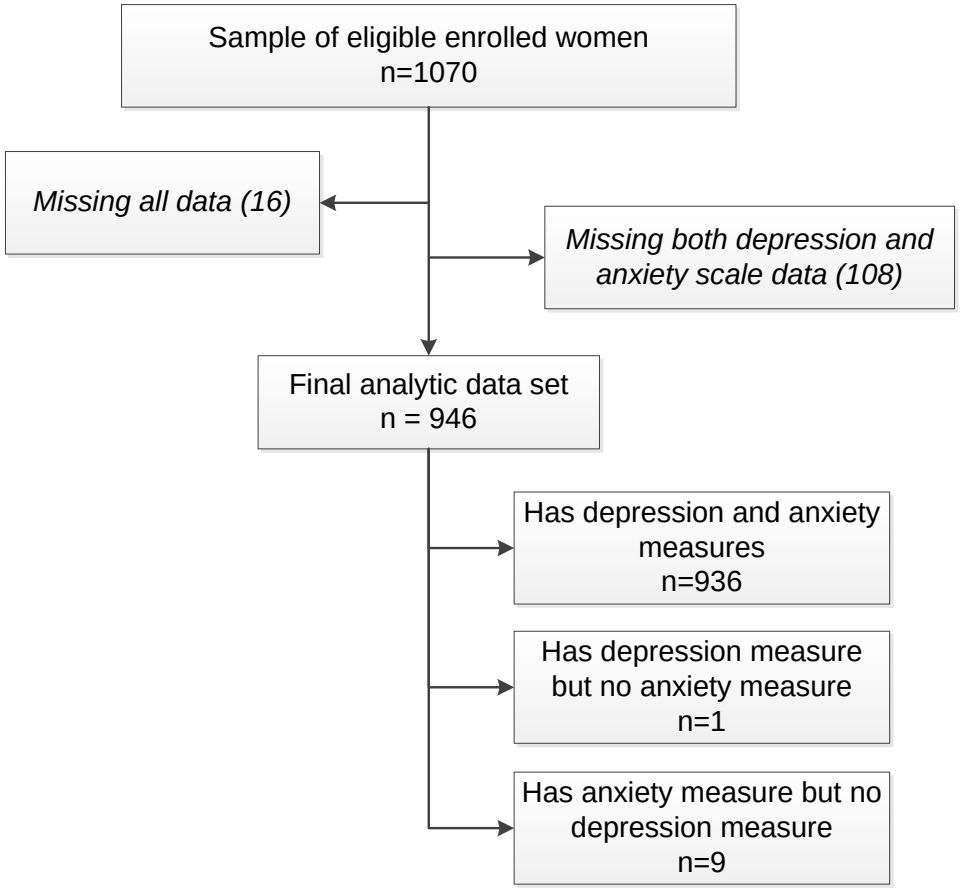

Figure 3.1 Consort Diagram of participating women included in the analytic data set

Baseline socio-demographic and health characteristics are presented in Table 3.1. The age of women in the study ranged from 18 to 44 years (mean=29.7). Most women (63%) were single or separated from their partners, 28% were primiparous and over half (52%) of the pregnancies were unplanned; 9% of women had smoked in the past 3 months and 10% of women had drunk alcohol since finding out they were pregnant, with 3.5% drinking more than 4 units of alcohol per week. A small percentage of women (3%) had previously been diagnosed with a mental illness. The prevalence of HIV in the sample was 29% (n=271), with 48% (n=128) of these women being diagnosed HIV-positive in the current pregnancy, and 52% (n=143) diagnosed prior to current pregnancy.

Table 3.1 Sample characteristics of mothers (n=946)

Maternal demographics	n	%
Maternal age		
Median [IQR]	29 [25,34]	-
Mother's education		
None or attended primary school	21	2.2
Attended Secondary	662	70.0
Tertiary and Professional training	251	26.5
Relationship status		
Single/widowed/separated	592	62.6
Married/cohabiting	352	37.2
Household: total number of people		
≤3	447	47.3
≥4	475	50.2
Household: people under 5 years		
No children under 5 years	599	63.3
Children under 5 years	321	33.9
Maternal socio-economics		
Asset score*		
Median [IQR]	5 [5-6]	
Maternal health characteristics		
Parity		
1 (first pregnancy)	266	28.1
2 (second pregnancy)	388	41.0
3+	280	29.6
Reproductive intention		
Unplanned pregnancy	488	51.6
Planned pregnancy	434	45.9
Smoked (last 3 months)		
No	863	91.2
Yes	82	8.7
Alcohol use (this pregnancy)		
No alcohol use	802	84.8
Weekly alcohol use	97	10.3
Mental illness (previous)		
No	920	97.3
Yes	26	2.8
Mental illness (current pregnancy)		
No	937	99
Yes	8	0.9
HIV status		
HIV negative	647	*68.4*
HIV positive: diagnosed in current pregnancy	128	13.5
HIV positive: diagnosed prior to conception	143	15.1

* Asset score rangers from 0 to 11 and is calculated by adding the items in the household including, electricity, radio, television, refrigerator, cell phone, personal computer, farm animals, agricultural land, bicycle, motorcycle/scooter and vehicle.

In terms of social support (Table 3.2), most women had a confidante and someone to help with a problem, and the majority could also talk to their partners. In terms of support outside of the home, three quarters of women belonged to an organisation such as a church, and half had a friend with a baby. Nearly all women (92%) reported

that the staff at the antenatal clinic they attend were helpful either some or all of the time.

Table 3.2 Social Support Questionnaire

	n	%
Practical support		
Nobody	70	7.4
Maybe	73	7.7
Yes	801	84.7
Missing	*2*	*0.2*
Confidante		
Nobody	56	5.9
Maybe	66	7.0
Yes	823	87
Missing	*1*	*0.1*
Partner is confidante		
No	50	5.3
Sometimes	210	22.2
Always	685	72.4
Missing	*1*	*0.1*
Clinic friendliness		
Clinic staff are not helpful	69	7.3
Clinic staff sometimes helpful	390	41.2
Clinic staff always helpful	478	50.5
Missing	*9*	*1.0*
Community support		
Does not belong to organisation	237	25.1
Belongs, attends irregularly	174	18.4
Belongs, attends regularly	523	55.3
Missing	*12*	*1.3*
Has a friend with a baby		
No friend with baby	486	51.4
Sees friend irregularly	115	12.2
See friend regularly	331	35.0
Missing	*14*	*1.5*

Examining the stressors reported by women (Table 3.3) we see that in the 6 months prior to the first assessment, economic stress was highest, with 75% of women reporting either being in debt, not having enough money for basics, or having to support family members in financial need. This was followed by family stress, with about half of all women (48%) reporting fighting with or being alienated from family, having a family member with a substance abuse problem or having a disabled family member. With regards to partnerships, 18% of women had recently experienced intimate partner violence or had broken up with their partner. A further 37% of women said that they felt their partner made their life harder - 80% of these women had recently experienced IPV, and 69% of them had recent breakups. Societal stress, in particular exposure to violence, was the least common stressor reported by women in

the cohort, with 12% of women reporting having witnessed a violent crime or being in danger of being killed.

Table 3.3 Antenatal stress questionnaire (in the last 6 months)

	n	%
In danger of being killed:		
Not in danger of being killed	899	95.0
In danger of being killed	47	5.0
By Criminals	*26*	*2.7*
By Policy/army	*5*	*0.5*
During political activities	*9*	*1*
Other	*7*	*0.7*
Missing	*0*	*0*
Witness violent crime		
No	850	89.9
Yes	90	9.5
Missing	*6*	*0.6*
Had debt that could not be repaid		
No	650	68.7
Yes	292	30.9
Missing	*4*	*0.4*
Unable to afford basics		
No	512	54.1
Yes	427	45.1
Missing	*7*	*0.7*
Unemployed more than 6 months (self or family member)		
No	300	31.7
Yes	643	68
Missing	*3*	*0.3*
Serious illness (self or family member)		
No	618	65.3
Yes	326	34.5
Missing	*2*	*0.2*
Death of family member		
No	706	74.6
Yes	239	25.3
Missing	*1*	*0.1*
Family member with disability		
No	780	82.5
Yes	*164*	*17.3*
Missing	*2*	*0.2*
Family member is substance user		
No	670	70.8
Yes	275	29.1
Missing	*1*	*0.1*
Break-up with partner		
No	814	86.1
Yes	129	13.6
Missing	*3*	*0.3*
Beaten by partner		

No	873	92.3
Yes	63	6.9
Missing	*8*	*0.9*
Alienation from family or friends		
No	755	79.8
Yes	188	19.9
Missing	*3*	*0.3*
Self or family member been arrested/ gone to court		
No	819	86.6
Yes	124	13.1
Missing	*3*	*0.3*
Provided monetary assistance / accommodation to others		
No	445	47.0
Yes	500	52.9
Missing	*1*	*0.1*
Been separated unwillingly from children		
No	882	93.2
Yes	37	3.9
Missing	*27*	*2.9*
Problems with other children		
No	634	67.0
Yes	47	5.0
No other child	247	26.1
Missing	*18*	*1.9*
Partner makes life harder		
No	590	62.4
Yes	353	37.3
Missing	*3*	*0.3*

3.3.2 Prevalence of antenatal depression and anxiety

Depression**:** 253/937 or 27.0% (95% CI 24.2-29.8) of women scored above the threshold for probable depression using the cut off of ≥13 on the EPDS.

Anxiety: 144/945 or 15.2% (95% CI 12.9-17.5) of women scored above the threshold for probable anxiety using the cut off of ≥12 on the 6-item short form of the STAI.

Comorbid Depression and Anxiety: 321/936 (34.3%) of women scored above the threshold for either depression or anxiety. When accounting for comorbidity we note that:

- Of 936 women with both depression and anxiety measures, 68 (7.3%) had co-morbid antenatal depression and anxiety.
- Out of the 253 women with antenatal depression, a quarter [68, 26.9%] also had anxiety
- Out of the 136 women with antenatal anxiety, half [68, 50.0%] also had antenatal depression.

3.3.3 Factors associated with antenatal depression

In the multivariate model (Table 3.4) no socio-demographic or socio-economic factors were associated with antenatal depression. Two health characteristics were significantly associated with increased odds of depression: As compared to primigravidas, mothers in their second pregnancy were 40% less likely to score above the threshold for depression; and women who had a current diagnosis of mental illness at baseline, had substantially increased odds of scoring above the threshold, although numbers were small (n=26/946, 2.8%) and confidence intervals wide. HIV was not significantly associated with either depression or anxiety in the final adjusted model.

In terms of social support, reporting a supportive relationship with a partner and having a confidante (someone to talk to) significantly decreased the odds of depression, as did reporting a helpful relationship with antenatal care nurses. If women belonged to a community organisation which offered them support (such as a church) but visited irregularly, then they had increased odds of depression.

Also in the multivariate analysis we see that amongst the stressors, difficulties in the partner relationship were strongly associated with women's odds of probable depression. If a woman reported that her partner made her life harder, her odds of depression increased more than threefold. Similarly, relationship stress (experiencing intimate partner violence and/or breaking up with her partner) increased the odds of depression, but this was attenuated when the perception that partners made their lives harder variable was included in the model. This is not surprising given that most women experiencing IPV reported that their partner made their life harder. Family stress and economic stress were also independently associated with increasing odds of depression.

The direction of relationships are similar to those evident in the literature although some commonly reported risk factors from the literature were significant in the univariate analysis only. For example: being tested HIV positive in the current pregnancy, having an unplanned pregnancy, a lack of practical support, and smoking were significantly associated with increased odds of depression in univariate, but not multivariate analysis. This suggests that these factors are explained by other variables in the model.

Table 3.4 Model 1: Depression univariate and multivariate logistic regression

	All available data (n=946)	Complete cases (n=800)	Complete cases (n=800)
	Univariate analysis OR [CI-CI] P>z	Univariate analysis OR [CI-CI] P>z	Multivariate analysis AOR [CI-CI] P>z
Maternal Demographics			
Age (continuous)	0.98 [0.95-1.01] 0.160	0.98 [0.95-1.01] 0.131	0.99 [0.95-1.02] 0.424
Attended Secondary	1.27 [0.46-3.53] 0.641	1.25 [0.40-3.90] 0.698	1.38 [0.35-5.50] 0.649
Tertiary and Professional training	0.91 [0.32-2.60] 0.859	0.92 [0.29-2.96] 0.888	1.03 [0.25-4.33] 0.968
Married/cohabiting	0.80 [0.59-1.08] 0.144	0.77 [0.55-1.06] 0.113	1.14 [0.76-1.72] 0.518
≥4 people in household	1.08 [0.80-1.44] 0.614	1.32 [0.96-1.81] 0.089	0.96 [0.62-1.48] 0.852
Children under 5 in household	1.30 [0.96-1.76] 0.092	**1.39 [1.01-1.92] 0.046**	1.26 [0.83-1.92] 0.273
Maternal socio-economics			
Asset score (continuous)	0.99 [0.90-1.08] 0.744	1.01 [0.92-1.12] 0.833	1.05 [0.93-1.18] 0.420
Maternal health characteristics			
Second pregnancy	0.72 [0.51-1.02] 0.062	0.70 [0.47-1.02] 0.065	**0.60 [0.37-0.95] 0.029**
Third+ pregnancy	0.72 [0.50-1.05] 0.092	0.80 [0.54-1.20] 0.287	0.78 [0.45-1.35] 0.373
Planned pregnancy	**0.72 [0.53-0.96] 0.026**	**0.68 [0.49-0.94] 0.018**	0.77 [0.53-1.12] 0.171
Smoked	**2.41 [1.51-3.84] 0.000**	**2.52 [1.48-4.26] 0.001**	1.52 [0.78-2.95] 0.220
Alcohol use	1.11 [0.69-1.79] 0.660	1.13 [0.68-1.88] 0.644	0.83 [0.45-1.54] 0.556
Mental illness - previous	1.97 [0.86-4.49] 0.107	1.99 [0.84-4.72] 0.120	1.00 [0.35-2.87] 0.995
Mental illness - current	**8.27 [1.66-41.25] 0.010**	**7.17 [1.38-37.25] 0.019**	**7.04 [1.02-48.44] 0.047**
HIV positive: diagnosed current pregnancy	**1.52 [1.01-2.28] 0.043**	**1.56 [1.00-2.43] 0.051**	1.17 [0.69-1.98] 0.566
HIV positive: diagnosed prior to conception	1.05 [0.70-1.58] 0.815	1.17 [0.76-1.80] 0.481	1.06 [0.64-1.76] 0.808
Social Support Questionnaire			
Has practical support	**0.33 [0.20-0.55] 0.000**	**0.33 [0.20-0.56] 0.000**	0.57 [0.30-1.08] 0.085
Has a confidante	**0.29 [0.16-0.52] 0.000**	**0.29 [0.16-0.52] 0.000**	**0.45 [0.21-0.93] 0.031**
Able to confide in partner	**0.46 [0.36-0.58] 0.000**	**0.29 [0.15-0.53] 0.000**	**0.43 [0.21-0.91] 0.026**
Clinic staff are helpful	**0.39 [0.24-0.65] 0.000**	**0.42 [0.24-0.73] 0.002**	**0.46 [0.24-0.90] 0.022**
Belongs to organisation, attends irregularly	**1.59 [1.03-2.45] 0.036**	**1.78 [1.11-2.86] 0.017**	**2.26 [1.30-3.95] 0.004**
Belongs to organisation, attends regularly	1.08 [0.75-1.54] 0.684	1.20 [0.81-1.77] 0.369	1.43 [0.90-2.28] 0.132
Sees friend with baby irregularly	1.11 [0.71-1.75] 0.647	1.14 [0.71-1.82] 0.597	0.91 [0.53-1.56] 0.724
Sees friend with baby regularly	0.98 [0.71-1.35] 0.905	0.89 [0.63-1.26] 0.512	0.79 [0.53-1.19] 0.261
Social Stress Questionnaire			
Martial stress (domestic violence/break up)	**3.45 [2.43-4.89] 0.000**	**3.14 [2.16-4.57] 0.000**	1.49 [0.96-2.33] 0.078
Perception that partner makes life harder	**4.15 [3.06-5.63] 0.000**	**4.34 [3.11-6.05] 0.000**	**3.33 [2.28-4.85] 0.000**
Family stress (conflict, illness/disability)	**2.32 [1.66-3.00] 0.000**	**2.41 [1.74-3.34] 0.000**	**1.78 [1.22-2.59] 0.003**
Economic stress (debt/insufficient resources)	**2.38 [1.60-3.53] 0.000**	**2.59 [1.66-4.03] 0.000**	**1.89 [1.15-3.12] 0.013**
Societal stress (witnessing/experience of violence)	**1.76 [1.18-2.63] 0.006**	**1.64 [1.05-2.57] 0.029**	1.14 [0.67-1.93] 0.623

Table 3.5 Model 2: Anxiety univariate and multivariate logistic regression

	All available data (n=946)	Complete cases (n=802)	Complete cases (n=802)
	Univariate analysis OR [CI-CI] P>z	Univariate analysis OR [CI-CI] P>z	Multivariate analysis[a] AOR [CI-CI] P>z
Maternal Demographics			
Age (continuous)	**0.95 [0.92-0.98] 0.001**	**0.95 [0.91-0.98] 0.002**	**0.95 [0.91-0.99] 0.021**
Attended Secondary	0.70 [0.23-2.14] 0.537	0.52 [0.17-1.64] 0.266	0.33 [0.10-1.14] 0.079
Tertiary and Professional training	0.88 [0.28-2.74] 0.824	0.68 [0.21-2.22] 0.527	0.45 [0.13-1.65] 0.230
Married/cohabiting	0.73 [0.50-1.07] 0.102	0.66 [0.44-1.01] 0.054	0.76 [0.47-1.22] 0.258
≥4 people in household	1.19 [0.83-1.71] 0.353	1.27 [0.86-1.88] 0.231	0.82 [0.51-1.34] 0.430
Children under 5 in household	**1.59 [1.10-2.30] 0.014**	**1.64 [1.11-2.43] 0.013**	**1.79 [1.12-2.87] 0.015**
Maternal socio-economics			
Asset score[b]	1.03 [0.92-1.15] 0.647	1.03 [0.91-1.17] 0.605	1.03 [0.90-1.18] 0.670
Maternal health characteristics			
Second pregnancy	0.68 [0.45-1.03] 0.071	**0.61 [0.38-0.97] 0.037**	0.66 [0.40-1.10] 0.110
Third+ pregnancy	**0.61 [0.38-0.96] 0.035**	0.63 [0.39-1.04] 0.072	0.92 [0.50-1.70] 0.796
Planned pregnancy	0.78 [0.54-1.13] 0.197	0.81 [0.55-1.20] 0.297	0.88 [0.57-1.34] 0.544
Smoked	1.67 [0.96-2.92] 0.071	1.74 [0.93-3.28] 0.083	1.32 [0.64-2.73] 0.453
Alcohol use	1.24 [0.71-2.16] 0.459	1.12 [0.59-2.09] 0.734	0.89 [0.45-1.77] 0.740
Mental illness - previous	1.01 [0.34-2.98] 0.983	1.14 [0.38-3.40] 0.812	0.81 [0.24-2.71] 0.729
Mental illness - current	0.79 [0.10-6.49] 0.828	0.95 [0.11-7.93] 0.960	0.76 [0.07-7.80] 0.818
HIV positive: diagnosed current pregnancy	0.85 [0.49-1.47] 0.554	0.93 [0.51-1.68] 0.801	0.99 [0.52-1.87] 0.973
HIV positive: diagnosed prior to conception	1.06 [0.65-1.74] 0.820	1.06 [0.63-1.80] 0.824	1.23 [0.70-2.17] 0.469
Social Support Questionnaire			
Has practical support	0.57 [0.32-1.03] 0.060	**0.49 [0.27-0.92] 0.026**	0.53 [0.26-1.07] 0.076
Has a confidante	0.57 [0.30-1.09] 0.091	0.65 [0.31-1.34] 0.243	0.90 [0.40-2.04] 0.803
Able to confide in partner	0.70 [0.34-1.43] 0.328	0.56 [0.27-1.17] 0.122	0.82 [0.37-1.84] 0.632
Clinic staff are helpful	0.62 [0.34-1.14] 0.124	0.53 [0.27-1.02] 0.055	0.50 [0.25-1.01] 0.053
Belongs to organisation, attends irregularly	1.09 [0.62-1.89] 0.771	1.14 [0.63-2.08] 0.660	1.21 [0.64-2.28] 0.550
Belongs to organisation, attends regularly	1.19 [0.77-1.83] 0.444	1.12 [0.70-1.80] 0.641	1.26 [0.76-2.10] 0.366
Sees friend with baby irregularly	1.15 [0.67-1.98] 0.605	1.19 [0.67-2.12] 0.553	1.01 [0.55-1.85] 0.982
Sees friend with baby regularly	0.93 [0.63-1.38] 0.728	1.00 [0.65-1.53] 0.994	0.98 [0.62-1.56] 0.938
Social Stress Questionnaire			
Martial stress (domestic violence/break up)	1.33 [0.86-2.06] 0.202	1.44 [0.90-2.30] 0.126	0.87 [0.51-1.49] 0.621
Perception that partner makes life harder	**1.45 [1.01-2.08] 0.043**	**1.60 [1.08-2.37] 0.018**	1.36 [0.87-2.11] 0.175
Family stress (conflict, illness/disability)	**1.80 [1.25-2.58] 0.002**	**1.87 [1.26-2.79] 0.002**	**1.75 [1.14-2.69] 0.011**
Economic stress (debt/insufficient resources)	1.19 [0.77-1.83] 0.429	1.21 [0.75-1.95] 0.425	1.00 [0.59-1.68] 0.986
Societal stress (witnessing/experience of violence)	1.20 [0.72-1.99] 0.488	1.10 [0.62-1.94] 0.756	0.85 [0.46-1.57] 0.600

3.3.4 Factors associated with antenatal anxiety

In the multivariate model (Table 3.5) having more children under the age of five years in the household significantly increased the odds of anxiety, as did family stress, while increasing age reduced odds of anxiety.

As with depression, the direction of effects for risk and protective factors were similar to the existing literature and factors such as increased number of pregnancies and having practical support reduced odds, while the perception that your partner was making your life harder increased odds but only in univariate and not multivariate analysis. HIV was not significantly associated with anxiety in univariate or multivariate analysis.

3.4 Discussion

3.4.1 The prevalence of antenatal depression and antenatal anxiety

We report a prevalence of 27% first trimester antenatal depression in a prospective pregnancy cohort of women residing in Soweto, South Africa. This is very similar to the prevalence (25%) reported in a meta-analysis of antenatal depression across all LMIC including mostly South American and Asian studies (12). However, it is almost three times higher than the previously reported antenatal prevalences from Africa (11%)(19) and is instead similar to reported prevalence's (23.4%) amongst high risk groups of HIV-infected pregnant women in Africa (51). In terms of antenatal anxiety we find a similar prevalence (15.2%) to that reported in a systematic review of African studies (14.8% (19).

That depression and anxiety emerge early in the pregnancy is important given that they may continue throughout the pregnancy, into the postnatal period and beyond. Antenatal depression and anxiety are associated with poor uptake of antenatal services (49), higher risks of premature birth, low birth weight, intrauterine growth restriction, child emotional and behavioural problems, cognitive difficulties and later depression (4).

3.4.2 The importance of the partner relationship

We find that a women's relationship with her partner has the strongest influence on her risk of antenatal depression and anxiety. Over a third (37%) of women reported that they felt their partners made their lives harder, and this was associated with a fourfold greater risk for antenatal depression. A smaller group of women reported more explicit levels of relationship stress (13.6% relationship termination; 6.9%

intimate partner violence), which substantially increased the risk of depression in univariate analysis, in line with previous research (88). When additional covariates, and particularly women's perception of whether their partners made their life harder, were included in the model the association with relationship stress was substantially reduced. This does not undermine the importance of relationship termination or IPV for mental health, rather it suggests that the impact of IPV could be largely explained by women who experience IPV feeling like their partners make their lives harder and other surrounding risks. Importantly, perceptions that partners made their life harder, was an independent risk factor in multivariate analysis, suggesting that this variable is important even outside of the context of IPV or relationship termination. Further research is needed to understand the meaning of perceiving that your partner makes life harder, and whether this reflects negatively biased perceptions that are a consequence of the depression itself(27) or objectively reflect the actual lived experiences of many women in these contexts. It also highlights the importance of including measures which potentially capture the subjective experience and impact of relationship problems as concurrent covariates in studies of antenatal depression and IPV (89).

Conversely, having a supportive partner can act as a buffer against maternal mental health problems in pregnancy(90) and in this analysis we show that being able to confide in your partner halves the risk for antenatal depression. This suggests that the engagement of male partners in antenatal services is important.

We provide evidence that problems in the partner relationship might not need to be explicit in order for it to have a substantial effect on a woman's mental health. A better understanding of these variables may inform the extent to which partner relationships may or may not be malleable to intervention and what intervention might be needed.

3.4.3 Social support and family impact

We illustrate that good social support provided by family and to some extent the broader social environment reduces the odds of both antenatal depression and anxiety. The literature on antenatal depression and anxiety suggests that social support is multifaceted (15) and can include instrumental (practical) support, informational support and emotional support. In this study having someone to talk to was somewhat more important than having people to practically help you, suggesting

that emotional support is as essential to coping with pregnancy as practical support, even in under-resourced communities. In this research we also show that family stress (family conflict, substance abuse or illness/disability in family) had the strongest association with antenatal anxiety, and was also associated with antenatal depression.

There is also evidence that families with a high burden of care for young children have increased odds of anxiety in pregnant women. Although we do not find this association in the existing literature, it may reflect the limited number of studies of antenatal anxiety, as we do see that in other LMIC research, having more children in the home has been associated with antenatal depression (91, 92).

3.4.4 Socio-economic status and economic stressors

The LMIC literature available on associations between antenatal depression and antenatal anxiety, and income or financial hardships shows contradictory evidence (12, 15). Although we find no significant association between SES (measured by asset ownership) and either antenatal depression or anxiety, similar to another South African study (24), we show that economic stress (being in debt or having insufficient resources) is associated with antenatal depression. It is possible that by including more detailed data on not only SES but also economic stressors, we are able to illustrate that regardless of SES, the presence of economic stressors (which is possible even if not poor but perhaps highly in debt) is associated with antenatal depression.

3.4.5 Role of HIV

In line with previous research (28) we report increased odds of depression in women with a recent HIV diagnosis in pregnancy, albeit it relatively small (OR 1.5). However, this was attenuated once wider social and familial stress and support were adjusted for, suggesting the impact of HIV is explained by the association between HIV and these contextual factors.

3.4.6 Impact of the study

This research adds weight to calls to make screening, treatment and prevention of antenatal depression and antenatal anxiety a public health priority for Africa.(12) As with the findings of other high risk groups, our findings demonstrate the value of boarder universal screening of mental health in pregnancy regardless of HIV status, socio-economic status or evidence of IPV. Although there is this evidence to support

universal screening for antenatal mental health disorders (93), challenges to feasibility in LMIC include time pressure and strained resources (94). The effectiveness of screening is also undermined if treatment cannot be accessed, which means that intervention in LMIC should be cost-effective and easily integrated into current services. Interventions which are integrated in routine antenatal care, and those delivered by non-specialist health care workers have been shown to be effective in LMIC (95, 96).

3.5 Strengths and Limitations

Strengths of the study include being a large contemporary cohort of women. The study uses validated measures and collects a large number of variables, which enables disentangling independence of multiple well-known risk factors. The analysis is limited in that data is from one timepoint and is thus cross-sectional. This means that we are unable to determine causal relationships, or establish the direction of effect of associations. It is also possible that results may reflect adjustments to pregnancy rather than persistent symptomology, and further research should examine later trimesters to explore these issues. Despite being well validated, the EPDS and STAI remain screening tools and not diagnostic measures. Although this is an urban sample, certain demographics, including a high number of single women, and high HIV prevalence, make it similar to other rural samples in other parts of SA, SSA or Africa. This however also makes it less generalizable to high income countries where pregnancies often occur within a stable relationship, and where HIV prevalence is low.

3.6 Conclusion

We illustrate for the first time in Sub-Saharan Africa that both depression and anxiety are prevalent in early pregnancy; risk for antenatal depression and antenatal anxiety is particularly high regardless of HIV status and importantly, that partnerships and family relationships are critical to ensuring women's mental health in pregnancy. Health interventions which engage and elicit family and partner support are thus potentially important for women during pregnancy which may also have benefits for delivery and offspring outcomes.

Chapter 4 : Antenatal depression and anxiety across pregnancy in urban South Africa[2]

[2] Redinger S, Pearson RM, Houle B, Norris SA, Rochat TJ. Antenatal depression and anxiety across pregnancy in urban South Africa. J. Affect. Disord. 2020; 277: 296-305.

4.1 Introduction

Perinatal depression and anxiety are both of public health concern given well documented negative consequences in both high income countries (HIC) (4) and low and middle income countries (LMIC) (12). Antenatal depression is associated with negative effects for pregnant women in terms of health behaviours, obstetric outcomes, suicide and substance use (4) and for offspring in terms of preterm birth, lower birth weight and later mental health risks (97). While anxiety is still relatively under researched, there is evidence that it is associated with child emotional well-being and behaviour, and disturbances in offspring neurodevelopment (4, 98). Systematic reviews in both HIC and LMIC have identified common stressors that are associated with both depression and/or anxiety during pregnancy including a previous history of mental illness, marital conflict, an absence of support, and pregnancy complications (15, 16). In LMIC settings however, given the higher level of contextual adversities (99), some additional factors have been shown to play a role including high rates of exposure to violence, extreme poverty, and epidemic levels of diseases such as HIV (5, 100).

Despite mounting evidence of the high triple burden of mental illness, HIV and violence on perinatal mental health in Africa (88) there is still a dearth of evidence from the region (79). In South Africa, research has shown high rates of both antenatal depression (30–40%) (28, 30, 32, 101, 102) and antenatal anxiety (14–18%) (42, 101). Current evidence in the region is limited by methodological shortcomings, including that there is substantial heterogeneity in the measurement of depression and anxiety making comparisons difficult; that most studies are cross-sectional and tend to only report on psychological problems late in pregnancy; and that almost no studies have examined anxiety on its own, or in the context of depression, despite these being known to be highly comorbid in HIC.

The Soweto First 1000 days (S1000) cohort is unique because it is one of only a handful of cohorts on the continent (and the only one in Southern Africa) to measure risk of both depression and anxiety in early and later pregnancy. Previously in this cohort, we demonstrated that risk for both depression (27%) and anxiety (15%) was already high in the first trimester of pregnancy, and that partner and family stressors played an important role in their early onset (101).

In this manuscript we investigate the incidence and persistence of both depression and anxiety across pregnancy; we identify risk factors associated with both transient and persistent symptoms of both; and we explore potentially modifiable mechanisms in the development of depression and anxiety in pregnancy.

4.2 Methods

The Soweto First 1000 days (S1000) cohort is based in the SAMRC/ Wits Developmental Pathways for Health Research Unit (DPHRU), at the Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, South Africa. The cohort is comprised of pregnant women aged 18–44 years (median 29 years) living in Soweto and accessing antenatal services at CHBAH.

The overall aim of S1000 was to understand associations between maternal health, foetal growth and infant outcomes using repeated measures collected at 6 time points during pregnancy, with a smaller sub-sample followed up biannually to the child's second birthday. Postnatal data collection was restricted to a selected subsample of women with complete pregnancy foetal growth (ultrasound) data for all six timepoints, and given potential selection bias this data is excluded from the current analysis.

4.2.1 Research context

Soweto is a large urban area of Johannesburg, with a population of 1.6 million people, who are predominantly Black African. Although Soweto is historically poor, it is undergoing rapid urbanisation, and is evidenced to have high rates of non-communicable disease including diabetes, high blood pressure and high blood cholesterol (68)

4.2.2 Recruitment

Women were consecutively recruited at the foetal medicine unit at CHBAH between 2014 and 2016. Inclusion criteria for S1000 were as follows: resident of Soweto, or the greater Soweto area, <20 weeks pregnant, no known diagnosis of epilepsy or diabetes at the time of recruitment, 18 years or older, and a naturally conceived singleton pregnancy. Psychological data was collected at two timepoints during pregnancy: at 14–18 weeks, and at 24–28 weeks - here after labelled time one (T1) and time two (T2), respectively. Of the 1055 women who completed baseline assessments, 938 had psychological data at T1; 704 had psychological data at T2. A

total of 649 had psychological data at both timepoints and are included in this analysis (see Fig 4.1).

All women provided written informed consent prior to their inclusion in the pregnancy component of the study (Soweto fetal Growth Study; SFGS). Ethical approval was obtained from the University of the Witwatersrand's Research Ethics Committee (Medical) for data collection [M120524] and data analysis [M180949].

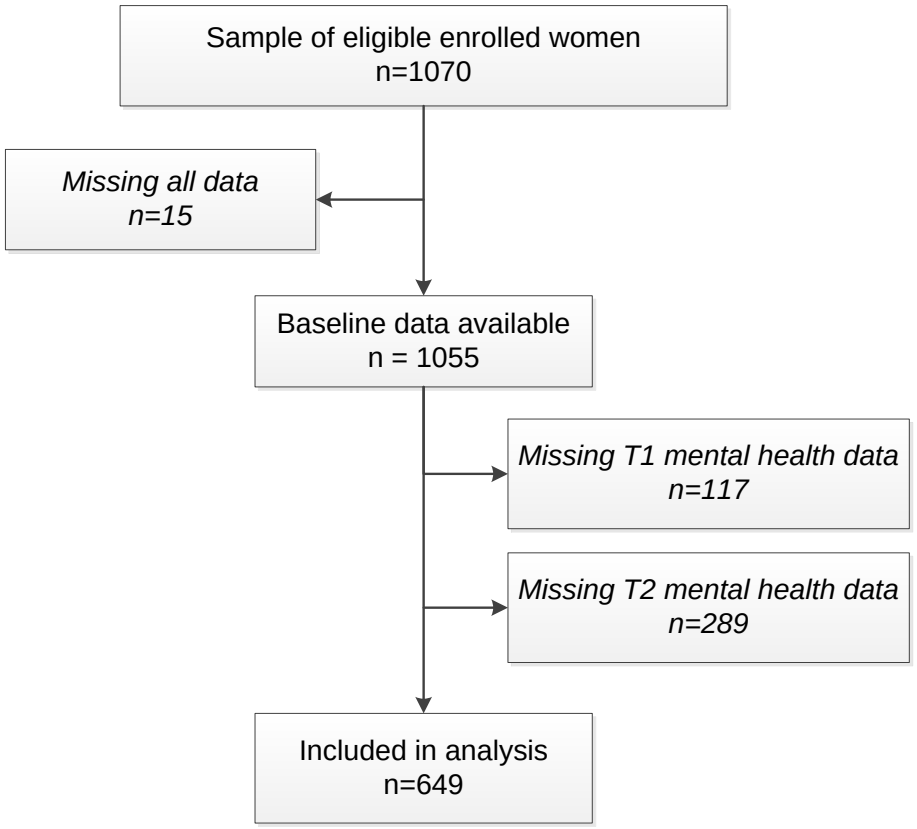

Figure 4.1 Consort diagram of women included in analytic dataset

4.2.3 Measures

We included a wide range of potential confounding variables, chosen a priori, based on both a theoretically-driven model (15) and previous analysis in this population (101).

Maternal health and socio-demographics

Study specific questionnaires collected self-report data on covariates including maternal age, education, relationship status, number of people living in the household, parity, reproductive intention, alcohol use, cigarette use, and previous mental illnesses. HIV status was self-reported and verified against clinical records.

Socio-economic status (SES)

SES was assessed using an 11-item self-report asset index derived from the Demographic and Health Surveys (DHS) (85). Scores range from 0 to 11, with a higher score representing higher SES.

Depression

The Edinburgh Postnatal Depression Scale (EPDS) is a widely used10-item measure of perinatal depression which has been validated for use during pregnancy in South Africa *(79)* and has previously shown good psychometric properties in this population (Cronbach's α 0.80) (101). Items are scored on a severity scale (0 to 3) and summed for a total possible score of 30. We used the standard cut-off score of ≥13/30 to indicate probable depression in this analysis (21, 80). While recognising that the ≥13/30 cut-off is used to establish clinical risk and does not provide a clinical diagnosis, we refer to probable depression as 'depression' in this manuscript for ease of reading.

Because anxiety symptoms are a common feature of depressive episodes in pregnant women, the EPDS is constructed to measure both depressive (7 items) and anxious (3 items) symptoms (103). Other research in South Africa using the EPDS and clinical interviews has not demonstrated adequate reliability of the 3-item anxiety subscale as a stand-alone measure of anxiety (78, 104). In this research depression (as measured by the EPDS) represents a single construct, including where present, anxious features.

Anxiety

The State Anxiety Inventory Short Form (STAI-6) is a 6-item version of the 20-item Spielberger State-Trait Anxiety Inventory Index, which has shown good internal consistency reliability and validity when correlated with the original scale (82, 105). This scale has been validated for use in perinatal populations (87), and was previously found to have an acceptable level of reliability in this population (Cronbach's α 0.64) (101). Items are scored on a severity scale (1–4) and summed for a total score of 24. We used a cut-off score of ≥12/24, which is the same cut-off ratio as the original STAI (>40/80) to indicate probable anxiety. As the STAI does not provide a clinical diagnosis of anxiety, we refer to probable anxiety as assessed using with measure as 'anxiety' in this manuscript for ease of reading.

Social support: A 9-item self-report questionnaire (84) previously used in this population, was used to identify the absence or presence of different aspects of social support including: people available to help, a confidante, being able to speak to her partner, belonging to a community organisation/ church and having a friend with a baby. Items were used as individual variables in the analysis.

Antenatal stress: A self-report stress questionnaire previously validated in this population (83, 84) collected data on the presence or absence of 16 different stressors in the 6 months prior to the interview (prenatal and antenatal). In line with previous research, we grouped the 10 items into four categories of stressors including: relationship stress (partner violence, relationship break-up); family stress (having a fight with/being alienated from family, family member with substance abuse problem, disabled family member); economic stress (being in debt, having too little money for basics, having to support family members in financial need); and societal stress (being in danger of being killed, witnessing a violent crime). Scores for each category were used as continuous variables.

All self-report questionnaires and scales were administered through an interview in English or in the participant's home language where required, by trained research assistants with at least 3 to 5 years data collection experience. Interviews were done in a private room within the DPHRU building at CHBAH.

4.2.4 Statistical analysis

Analysis was performed in StataSE version 15 (86)and MPlus version 8.3 (106). Descriptive statistics and prevalences are reported using all available data at T1 and T2, however statistical models were restricted to those women with mental health data at both timepoints (n = 649).

Data transformation

Using a standard approach missing items on psychological scales were imputed if ≤20% of the scale items were missing, using the median score of available scale items. Participants with >20% of their psychological scales items missing were excluded.

Total scores on the EPDS and STAI were dichotomised to classify participants as meeting thresholds for depression and/ or anxiety using recognised cut-offs for probable cases on screening tools (≥13 EPDS, ≥12 STAI). Point prevalence of

depression, anxiety and comorbidity were calculated using these variables. Comorbidity was calculated as the presence of both disorders at each timepoint.

Participants were then categorised into three mutually exclusive groups for both depression and anxiety caseness. Groups were defined by the presence or absence of probable cases across the two timepoints in pregnancy: 0: Absence during pregnancy (None); 1: Present at T1 but not at T2 (Early-recover); 2: not present at T1 but present at T2 (Late-onset); and 3: present at both T1 and T2 (Persistent).

Descriptive statistics

Descriptive statistics summarised sample characteristics. Sensitivity analysis comparing baseline characteristics of participants included in the final analysis versus those excluded were completed using non-parametric tests (Chi-Square, Wilcoxon rank-sum). Internal consistency of EPDS and STAI-6 was examined by calculating the average inter-item correlation using Cronbach's alpha.

Multinomial logistic regressions

Multinomial logistic regression models were used to determine factors associated with belonging to each of the 3 groups (early-recover, late-onset, persistent) for both depression and anxiety, with the “never present” group as the reference group.

Only T1 variables were used as exposures in the multinomial logistic regression models as our outcome variables (groups by timing of onset and recovery) were created using outcome variables at T1 and T2. To determine whether stress and support variables differed significantly from T1 to T2 we used z-tests and t-tests respectively (Supplementary Table 4.1 in Appendix E). We also did cross-sectional logistic regression analyses of T2 depression and anxiety cases using T2 support and stress variables to determine associations at later pregnancy independent of timing of onset or duration (Supplementary Table 4.2. in Appendix E)

Cross-lagged panel analysis

Cross-lagged panel analysis was used to explore the direction of effect between depression and anxiety and the 4 categories of stress, both collected at the two timepoints. These analyses were performed as path analyses within a structural equation modelling framework using MPlus version 8.3 (106), where T2 variables

were regressed onto T1 variables while accounting for T1 and T2 within variable correlations.

To increase power, we used continuous total scores for the depression and anxiety scales. While family and economic stress factors were already continuous and remained unchanged from previous analyses, for this analysis we transformed the remaining two stress variables (marital and societal stress) to be used as stress factors. The partner stress factor was created by combining the marital stress variable (partner violence, relationship break-up) and the “my partner makes my life harder” questionnaire item. Similarly, a continuous societal stress factor was created by combining the societal stress variable (being in danger of being killed, witnessing a violent crime) with an absence of practical support (created by reverse scoring the presence of practical support variable).

4.3 Results

4.3.1 Sample

Baseline sample characteristics are shown in Table 4.1. The median age of women in the cohort was 29 (IQR 25–34) years, with the majority being single and having completed secondary school. Half of the cohort lived in smaller households of 3 or fewer people. Only a small percentage (2.6%, *n* = 17) of women reported having been diagnosed with a mental illness previously. Sensitivity analysis found that women included in this analysis (*n* = 649) had a slightly higher mean asset score (5.5, SD 1.5) than those excluded (5.2, SD 1.8) representing a score difference of 0.3 (or approximately one third of an asset).

Table 4.1 Comparison of women in S1000 study by inclusion/ exclusion in the analytic dataset

	Total (n=1055)			Excluded (n=406)			Included (n=649)			p-value
	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)	n	%	
Maternal demographics										
Maternal age	29.8 [5.9]			30.0 [5.9]			29.6 [5.9]			0.326
Mother's education										
None or attended up to secondary		773	73.3		309	76.1		464	71.5	0.086
Tertiary & Professional training		270	25.6		92	22.7		178	27.4	
Missing		*12*	*1.1*		*5*	*1.2*		*7*	*1.1*	
Relationship status										
Single		656	62.2		249	61.3		407	62.7	0.666
Married/cohabiting		397	37.6		156	38.4		241	37.1	
Missing		*2*	*0.2*		*1*	*0.2*		*1*	*0.2*	
Household: total people										
≤3		493	46.7		186	45.8		307	47.3	0.665
≥4		527	50.0		206	50.7		321	49.5	
Missing		*35*	*3.3*		*14*	*3.4*		*21*	*3.2*	
Household: people <5 years										
No children under 5 years		632	59.9		211	52.0		421	64.9	0.198
Children under 5 years		344	32.6		129	31.8		215	33.1	
Missing		*79*	*7.5*		*66*	*16.3*		*13*	*2.0*	
Asset score*	5.4 [1.6]			5.2 [1.8]			5.5 [1.5]			**0.005**
Pregnancy and health characteristics										
Parity										
1 (first pregnancy)		293	27.8		119	29.3		174	26.8	0.355
2 (second pregnancy)		749	71.0		281	69.2		468	72.1	
Missing		*13*	*1.2*		*6*	*1.5*		*7*	*1.1*	
Reproductive intention										
Unplanned pregnancy		514	48.7		181	44.6		333	51.3	0.811

Planned pregnancy		464	44.0		160	39.4		304	46.8	
Missing		*77*	*7.3*		*65*	*16.0*		*12*	*1.8*	
Smoked (last 3 months)										
No		962	91.2		370	91.1		592	91.2	0.837
Yes		91	8.6		34	8.4		57	8.8	
Missing		*2*	*0.2*		*2*	*0.5*		*0*	*0.0*	
Alcohol use (this pregnancy)										
No alcohol use		898	85.1		352	86.7		546	84.1	0.071
Weekly alcohol use		106	10.1		32	7.9		74	11.4	
Missing		*51*	*4.8*		*22*	*5.4*		*29*	*4.5*	
Mental illness (previous)										
No		1022	96.9		390	96.1		632	97.4	0.318
Yes		32	3.0		15	3.7		17	2.6	
Missing		*1*	*0.1*		*1*	*0.2*		*0*	*0.0*	
HIV status										
HIV-negative		704	66.7		260	64.0		444	68.4	0.137
HIV-positive		323	30.6		135	33.3		188	29.0	
Missing		*28*	*2.7*		*11*	*2.7*		*17*	*2.6*	

4.3.2 Descriptive analysis

We determined cases of probable depression, anxiety and co-morbidity as follows:

Depression: The EPDS showed good internal consistency at both timepoints (Cronbach's α T1: 0.80 and T2: 0.81). At T1: 253/938 (27.0%) scored above the cut-off of ≥13 for depression, and at T2: 179/704 (25.4%). When restricted to women who had data at both timepoints prevalences were similar: T1: 186/649, 28.7% (95%CI 25.2–32.3); T2: 160/649, 24.7% (95%CI 21.4–28.2)

Anxiety: The STAI showed fair internal consistency at both timepoints (Cronbach's α T1: 0.65 and T2: 0.71). At T1: 137/938 (14.6%) scored above the ≥12 cut-off and at T2: 129/704 (18.3%). When restricted to women who had data at both timepoints prevalences were again similar: T1: 96/649, 14.6% (95%CI 12.1–17.8); T2: 115/649, 17.7% (95%CI 14.9–20.9)

Comorbidity: At T1: 68/938 (7.2%) and at T2: 70/704 (9.9%) of women met criteria for both depression and anxiety. When restricted to women who had data at both timepoints, prevalences were similar: T1: 49/649, 7.6% (95%CI 5.6–9.9); T2: 63/649, 9.7% (95%CI 7.5–12.2).

Onset and persistence: Women meeting criteria for both depression and anxiety were categorised into three groups based on timing of symptoms (See Table 4.2) in order to examine variations across pregnancy in terms of timing of onset, and persistence of the disorders.

Table 4.2 Participants grouped by timing of onset and duration of depression and anxiety across pregnancy (n=649)

	Depression n (%)	**Anxiety** n (%)
Never met threshold	385 (59.3)	472 (72.7)
Early-recover	104 (16.0)	62 (9.6)
Late-onset	78 (12.0)	81 (12.5)
Persistent	82 (12.6)	34 (5.2)

Covariates

For most women rates of marital and social support (including having a confidante, your partner being a confidante and friendly health care staff) were consistently high across pregnancy, while only half of women regularly accessed community support and about a third had a friend with a baby who they saw regularly. There were decreases in almost all categories of stressors from T1 to T2, most notably in family stress (T1: 0.65, T2: 0.53, p <0.001), economic stress (T1: 1.3, T2: 1.11, p <0.001) and marital stress (T1: 0.20, T2: 0.16, p = 0.010) (Supplementary Table 4.1 Appendix E). The number of women reporting that their partner “makes their life harder” increased over the pregnancy from 39% (T1) to 44% (T2) (p = 0.042).

4.3.3 Factors associated with transient, late onset or persistent depression

The adjusted multinominal regression models for depression are presented in Table 4.3.

Early-recover depression: The factors associated with belonging to this group were largely partner and family related. We found that being married/ cohabiting with partner (RR1.87 95% CI [1.0–3.4] p = 0.038), feeling their partner made their life harder (RR 2.48 95% CI [1.4–4.4] p = 0.002), and family stress (RR 1.42 95% CI [1.0–2.0] p = 0.040) were associated with increased risk, while having practical support (RR 0.32 95% CI [0.1–0.9] p = 0.024) were associated with decreased risk.

Late onset depression: No factors were associated with increased risk in the adjusted model, however, having practical support (RR 0.28 95% CI [0.1–0.9] p = 0.027) was associated with decreased risk for late onset depression.

Table 4.3 Factors associated with depression and anxiety by pattern of onset and recovery across pregnancy, an adjusted multinomial regression model (n=524)

	Depression			Anxiety		
	Early Recover	**Late Onset**	**Persistent**	**Early Recover**	**Late Onset**	**Persistent**
	aRR [CI] p	**aRR [CI] p**	**aRR [CI] p**	**aRR [CI] p**	**aRR [CI] p**	**aRR [CI] p**
Age*	0.95 [0.9-1.0] 0.073	**0.93 [0.9-1.0] 0.016**	0.99 [0.9-1.1] 0.832	0.95 [0.9-1.0] 0.131	1.00 [0.9-1.1] 0.958	0.96 [0.9-1.0] 0.300
Education						
Primary/ secondary	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Tertiary/ professional	1.10 [0.6-2.1] 0.757	0.86 [0.4-1.7] 0.660	0.49 [0.2-1.1] 0.092	1.12 [0.5-2.4] 0.761	1.27 [0.7-2.4] 0.468	**2.58 [1.0-6.7] 0.050**
Relationship status						
Single	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Married/ cohabiting	**1.87 [1.0-3.4] 0.038**	1.17 [0.6-2.2] 0.619	1.19 [0.6-2.4] 0.626	0.71 [0.3-1.5] 0.354	1.10 [0.6-2.0] 0.765	0.79 [0.3-2.1] 0.630
People in household						
≤3	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
≥4	0.95 [0.5-1.7] 0.878	1.23 [0.7-2.3] 0.509	1.05 [0.5-2.1] 0.894	1.04 [0.5-2.1] 0.921	1.36 [0.8-2.4] 0.303	1.07 [0.4-2.6] 0.884
Children < 5 years						
No children < 5 years	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Children <5 years	1.39 [0.8-2.5] 0.280	1.23 [0.7-2.3] 0.504	1.28 [0.6-2.6] 0.480	1.68 [0.9-3.3] 0.132	0.55 [0.3-1.0] 0.069	1.59 [0.6-4.0] 0.322
Asset score*	0.86 [0.7-1.1] 0.157	0.91 [0.7-1.1] 0.410	0.83 [0.7-1.1] 0.133	1.25 [0.9-1.6] 0.113	1.00 [0.8-1.3] 0.967	0.76 [0.6-1.0] 0.059
Parity						
1st pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
2nd+ pregnancy	0.70 [0.4-1.4] 0.301	1.56 [0.7-3.4] 0.257	**0.47 [0.2-1.0] 0.047**	1.04 [0.5-2.3] 0.915	1.16 [0.6-2.4] 0.682	0.47 [0.2-1.2] 0.102
Reproductive intention						
Unplanned pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]		1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Planned pregnancy	0.72 [0.4-1.3] 0.253	0.75 [0.4-1.3] 0.334	0.73 [0.4-1.4] 0.351	0.72 [0.4-1.4] 0.334	0.89 [0.5-1.6] 0.696	1.39 [0.6-3.3] 0.445
Smoked (last 3 months)						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.61 [0.2-1.9] 0.384	0.62 [0.2-2.6] 0.514	0.85 [0.3-2.5] 0.774	1.55 [0.5-4.9] 0.459	0.41 [0.1-1.6] 0.199	0.71 [0.2-2.9] 0.637
Alcohol use						
No alcohol use	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]

Weekly alcohol use	0.95 [0.4-2.3] 0.903	1.40 [0.6-3.4] 0.461	0.79 [0.3-2.3] 0.672	0.73 [0.2-2.2] 0.580	1.77 [0.8-4.1] 0.179	2.27 [0.7-7.3] 0.170
Mental illness (previous)						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1.88 [0.5-7.6] 0.374	1.92 [0.3-10.8] 0.460	2.62 [0.5-12.7] 0.231	-	**4.82 [1.5-16.0] 0.010**	1.53 [0.2-15.6] 0.718
HIV status						
HIV Negative	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
HIV positive	1.42 [0.8-2.6] 0.252	1.15 [0.6-2.3] 0.675	1.22 [0.6-2.4] 0.566	1.10 [0.5-2.2] 0.788	0.65 [0.3-1.3] 0.216	1.49 [0.6-3.8] 0.401
Antenatal stressors**						
Marital stress	1.26 [0.7-2.3] 0.444	0.53 [0.2-1.3] 0.173	1.70 [0.9-3.1] 0.079	0.77 [0.4-1.6] 0.466	0.96 [0.5-1.9] 0.907	1.32 [0.6-3.1] 0.520
Family stress	**1.42 [1.0-2.0] 0.040**	0.74 [0.5-1.2] 0.182	1.38 [0.9-2.0] 0.100	1.25 [0.8-1.9] 0.257	1.40 [1.0-2.0] 0.065	**1.71 [1.1-2.7] 0.027**
Economic stress	1.20 [0.9-1.6] 0.234	1.16 [0.8-1.6] 0.354	1.26 [0.9-1.8] 0.203	1.16 [0.8-1.6] 0.404	0.93 [0.7-1.3] 0.646	0.76 [0.5-1.2] 0.280
Societal stress	1.26 [0.6-2.5] 0.507	0.82 [0.3-2.0] 0.656	1.78 [0.9-3.6] 0.109	0.64 [0.3-1.6] 0.329	0.99 [0.5-2.0] 0.985	1.31 [0.5-3.5] 0.591
Has practical support						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	**0.32 [0.1-0.9] 0.024**	**0.28 [0.1-0.9] 0.027**	**0.26 [0.1-0.8] 0.013**	0.64 [0.2-2.0] 0.444	0.82 [0.3-2.4] 0.719	**0.18 [0.1-0.6] 0.004**
Has confidante						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.49 [0.2-1.4] 0.189	3.04 [0.3-27.1] 0.319	1.11 [0.3-4.1] 0.873	0.49 [0.1-1.7] 0.269	0.59 [0.2-1.9] 0.369	5.50 [0.4-69.4] 0.188
Partner is confidante						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1.06 [0.3-3.8] 0.935	2.04 [0.2-16.8] 0.507	**0.30 [0.1-0.9] 0.028**	1.42 [0.3-5.8] 0.626	0.92 [0.3-3.3] 0.898	0.44 [0.1-1.8] 0.249
Clinic staff are friendly						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.55 [0.2-1.3] 0.180	2.30 [0.5-10.5] 0.281	0.63 [0.2-1.8] 0.402	1.08 [0.3-3.5] 0.891	1.49 [0.5-4.7] 0.500	0.36 [0.1-1.2] 0.108
Partner makes life harder						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	**2.48 [1.4-4.4] 0.002**	1.07 [0.6-2.0] 0.827	**5.92 [3.0-11.8] 0.000**	1.13 [0.6-2.3] 0.722	1.14 [0.6-2.1] 0.667	0.96 [0.4-2.4] 0.927
Community organisation						
Does not attend/ irregularly	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]

Attends regularly	1.00 [0.6-1.7] 0.998	0.90 [0.5-1.6] 0.734	0.69 [0.4-1.3] 0.248	0.76 [0.4-1.4] 0.404	0.62 [0.4-1.1] 0.093	1.08 [0.5-2.6] 0.864
Has friend with baby						
No or sees irregularly	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes, sees regularly	1.24 [0.7-2.2] 0.458	1.14 [0.6-2.1] 0.665	0.86 [0.4-1.7] 0.654	1.07 [0.6-2.1] 0.838	1.35 [0.8-2.4] 0.303	1.59 [0.7-3.8] 0.298

* Age and asset score are continuous variables; **Antenatal stressors are continuous scores

Persistent depression: Having a partner perceived to make one's life harder (RR 5.92 95% CI [3.0–11.8] p <0.001) was associated with an increased risk of persistent depression. Similarly being able to confide in one's partner (RR 0.30 95% CI [0.1–0.9] p = 0.028) was associated with decreased risk along with reporting practical support (RR 0.26 95% CI [0.1–0.8] p = 0.013), and it not being the first pregnancy (RR 0.47 95% CI [0.2–1.0] p = 0.047).

The unadjusted multinominal regression models are presented in Supplementary Table 4.3 (Appendix E) showing that higher level of education, economic stressors and smoking did not remain significant in adjusted models. Having a confidante, a friendly clinic and links to a community organisation were attenuated support variables in the adjusted models.

4.3.4 Factors associated with transient, late onset or persistent anxiety

The adjusted multinominal regression models for anxiety are presented in Table 3.3.

Early-recover anxiety: No factors were associated with belonging to this group in the adjusted models.

Late-onset anxiety: History of mental illness (RR 4.82 95% CI [1.5–16.0] p = 0.010) was the only factor associated with increased risk of late-onset anxiety.

Persistent anxiety: Family stress (RR 1.71 95% CI [1.1–2.7] p = 0.027) and tertiary level of education (RR 2.58 95% CI [1.0–6.7] p = 0.050) were associated with increased risk of persistent anxiety (although confidence intervals for the latter are close to 1). Practical support was the only factor associated with a decreased risk of persistent anxiety (RR 0.18 95% CI [0.1–0.6] p = 0.004).

In the unadjusted multinominal regression models for anxiety (see supplementary Table 4.4 in Appendix E) increasing age, asset score, parity and links to a community support organisation were associated with decreased risk in the persistent and late-onset anxiety group. Having children under 5 in the home was associated with increased risk for early pregnancy anxiety (early-recover) only.

4.3.5 Cross-lagged path analysis

Using repeated measures of depression and anxiety at early (T1) and late (T2) pregnancy we examined the direction of effect between these constructs, and stressors at T1 and T2.

The regression and correlation coefficients of the cross-lagged models for depression are shown in Tables 4.4 and Figure 4.2; and for anxiety in Table 4.5 and Figure 4.3.

Depression: All correlation coefficients between measures taken at the same time point are positive, suggesting that perceived stress and depressive scores are positively associated. This was strongest for depressive scores and partner stress at T1 [B (SE) = 0.368 (0.034) p <0.001].

Autoregressive path coefficients provide evidence of a large component of stability across the two timepoints of depression across pregnancy.

Cross-lagged paths suggest depression in early pregnancy is associated with later stressors over and above the baseline correlation and stability of depression. There is strong evidence of a direct effect of early depression on later family stress [B (SE) = 0.170 (0.036) p <0.001]. The cross-lagged paths between early depression to later partner, economic and societal stress suggest that there is evidence for paths in both directions.

Anxiety: The correlation coefficients between measures of anxiety and stress taken at the same timepoint suggest that anxiety is correlated at both timepoints with partner stress T1: [0.109 (0.039) p = 0.005] T2: [0.170 (0.038) p <0.001] and family stress T1: [0.088 (0.039) p = 0.024] T2: [0.207 (0.038) p <0.001]. Anxiety is not correlated with economic stress in early pregnancy, but shows a weak correlation in late pregnancy [0.119 (0.039) p = 0.002]. Anxiety is also not correlated with societal stress in early pregnancy, and only weakly correlated in later pregnancy [0.090 (0.040) p = 0.024].

Autoregressive path coefficients provide evidence of a large component of stability across the two timepoints of anxiety across pregnancy.

Cross-lagged paths suggest a direct effect of early family stress on later anxious symptoms [B (SE) = 0.086 (0.038) p <0.025].

Table 4.4 Standardised estimates for cross-lagged panel models of depression and stress

		Est	SE	CI	CI	p-value
PARTNER STRESS						
Correlations	EPDS_T1 on PARTNER_T1	0,368	0,034	0,30	0,44	0,000
	EPDS_T2 on PARTNER_T2	0,253	0,037	0,18	0,33	0,000
Autoregressive paths	EPDS_T2 on EPDS_T1	0,393	0,036	0,32	0,46	0,000
	PARTNER_T2 on PARTNER_T1	0,438	0,034	0,37	0,51	0,000
Crosslagged paths	PARTNER_T1 on EPDS_T2	0,065	0,038	-0,01	0,14	0,091
	EPDS_T1 on PARTNER_T2	0,096	0,037	0,02	0,17	**0,010**
FAMILY STRESS						
Correlations	EPDS T1 on FAMILY_T1	0,273	0,036	0,20	0,34	0,000
	EPDS_2 on FAMILY_T2	0,200	0,038	0,13	0,27	0,000
Autoregressive paths	EPDS_T2 on EPDS_T1	0,398	0,034	0,33	0,47	0,000
	FAMILY_T2 on FAMILY_T1	0,400	0,034	0,33	0,47	0,000
Crosslagged paths	FAMILY_T1 on EPDS_T2	0,069	0,037	-0,00	0,14	0,063
	EPDS_T1 on FAMILY_T2	0,170	0,036	0,10	0,24	**0,000**
ECONOMIC STRESS						
Correlations	EPDS_T1 on ECONOMIC_T1	0,261	0,037	0,19	0,33	0,000
	EPDS_T2 on ECONOMIC_T2	0,156	0,039	0,08	0,23	0,000
Autoregressive paths	EPDS_T2 on EPDS_T1	0,403	0,034	0,34	0,47	0,000
	ECONOMIC_T2 on ECONOMIC_T1	0,424	0,033	0,36	0,49	0,000
Crosslagged paths	ECONOMIC_T1 on EPDS_T2	0,054	0,037	-0,02	0,13	0,144
	EPDS_T1 on ECONOMIC_T2	0,085	0,036	0,01	0,16	**0,020**
SOCIETAL STRESS						
Correlations	EPDS_T1 on SOCIETAL_T1	0,199	0,038	0,13	0,27	0,000
	EPDS_T2 on SOCIETAL_T2	0,075	0,040	-0,00	0,15	0,058
Autoregressive paths	EPDS_T2 on EPDS_T1	0,403	0,033	0,34	0,47	0,000
	SOCIETAL_T2 on SOCIETAL_T1	0,157	0,039	0,08	0,23	0,000
Crosslagged paths	SOCIETAL_T1 on EPDS_T2	0,069	0,037	-0,00	0,14	0,061
	EPDS_T1 on SOCIETAL_T2	0,084	0,039	0,01	0,16	**0,032**

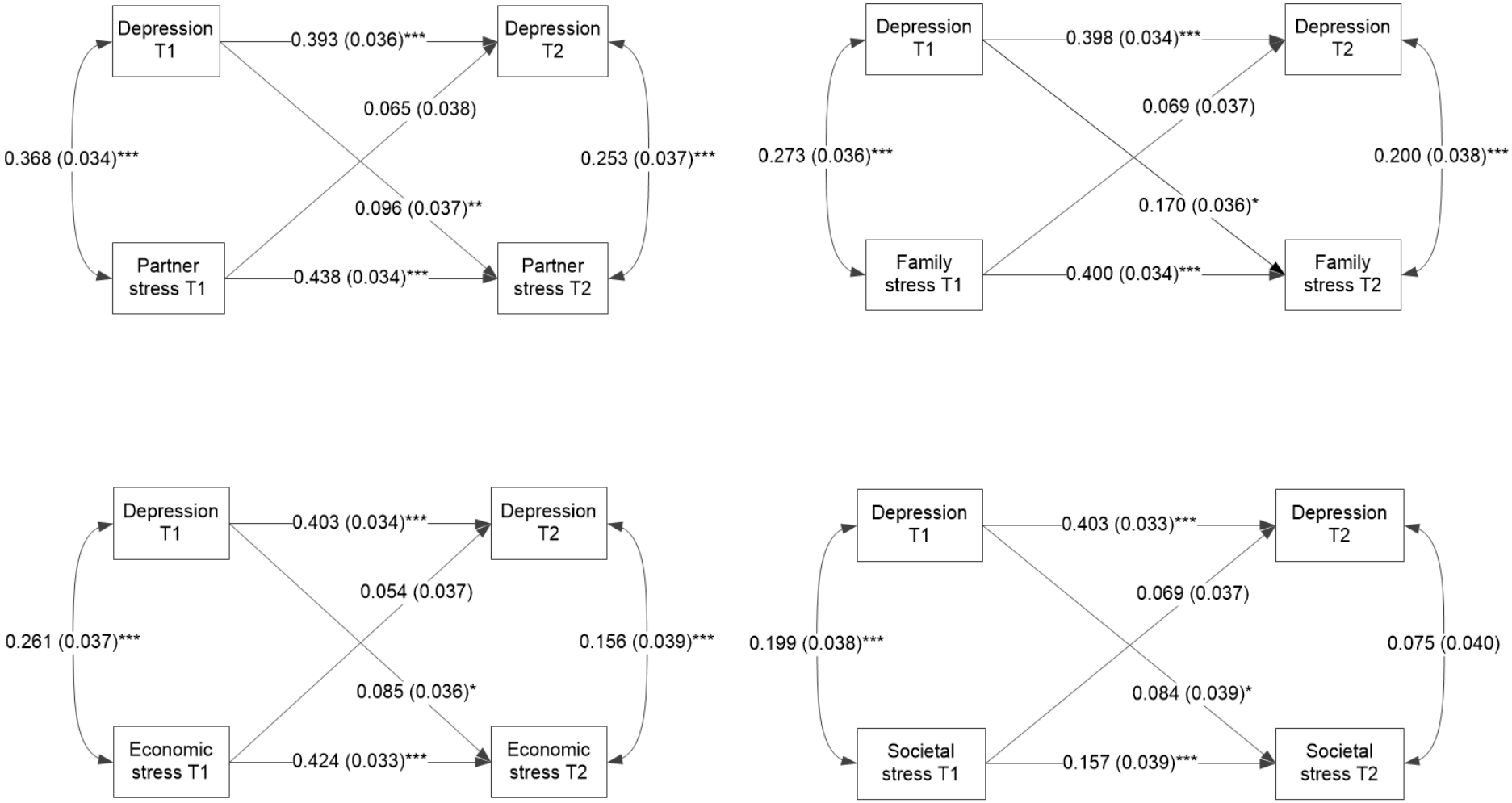

Figure 4.2 Cross-lagged panel model of depresssion and partner, family, economic and societal stress

Table 4.5 Standardised estimates for cross-lagged panel models of anxiety and stress

		Est	SE	CI	CI	p-value
PARTNER STRESS						
Correlations	ANXIETY_T1 on PARTNER_T1	0,109	0,039	0,03	0,19	0,005
	ANXIETY_T2 on PARTNER _T2	0,170	0,038	0,10	0,24	0,000
Autoregressive paths	ANXIETY_T2 on ANXIETY_T1	0,228	0,037	0,16	0,30	0,000
	PARTNER_T2 on PARTNER_T1	0,467	0,031	0,41	0,53	0,000
Crosslagged paths	ANXIETY_T2 on PARTNER_T1	0,055	0,038	-0,02	0,14	0,150
	PARTNER_T2 on ANXIETY_T1	0,047	0,035	-0,02	0,12	0,176
FAMILY STRESS						
Correlations	ANXIETY_T1 on FAMILY_T1	0,088	0,039	0,01	0,16	0,024
	ANXIETY_T2 on FAMILY_T2	0,207	0,038	0,13	0,28	0,000
Autoregressive paths	ANXIETY_T2 on ANXIETY_T1	0,226	0,037	0,15	0,30	0,000
	FAMILY_T2 on FAMILY_T1	0,446	0,032	0,38	0,51	0,000
Crosslagged paths	ANXIETY_T2 on FAMILY_T1	0,086	0,038	0,01	0,16	**0,025**
	FAMILY_T2 on ANXIETY_T1	0,026	0,035	-0,04	0,09	0,461
ECONOMIC STRESS						
Correlations	ANXIETY_T1 on ECONOMIC_T1	-0,040	0,039	-0,12	0,04	0,312
	ANXIETY_T2 on ECONOMIC_T2	0,119	0,039	0,04	0,20	0,002
Autoregressive paths	ANXIETY_T2 on ANXIETY_T1	0,236	0,037	0,16	0,31	0,000
	ECONOMIC_T1 on ECONOMIC_T2	0,446	0,032	0,38	0,51	0,000
Crosslagged paths	ANXIETY_T2 on ECONOMIC_T1	0,049	0,038	-0,03	0,12	0,206
	ECONOMIC_T1 on ANXIETY_T1	0,004	0,035	-0,06	0,07	0,915
SOCIETAL STRESS						
Correlations	ANXIETY_T1 on SOCIETAL_T1	0,068	0,039	-0,01	0,14	0,084
	ANXIETY_T2 on SOCIETAL_T2	0,090	0,040	0,01	0,17	0,024
Autoregressive paths	ANXIETY_T2 on ANXIETY_T1	0,233	0,037	0,16	0,31	0,000
	SOCIETAL_T1 on SOCIETAL_T2	0,174	0,039	0,10	0,25	0,000
Crosslagged paths	ANXIETY_T2 on SOCIETAL_T1	0,012	0,038	-0,06	0,09	0,746
	SOCIETAL_T1 on ANXIETY_T1	0,016	0,039	-0,06	0,09	0,685

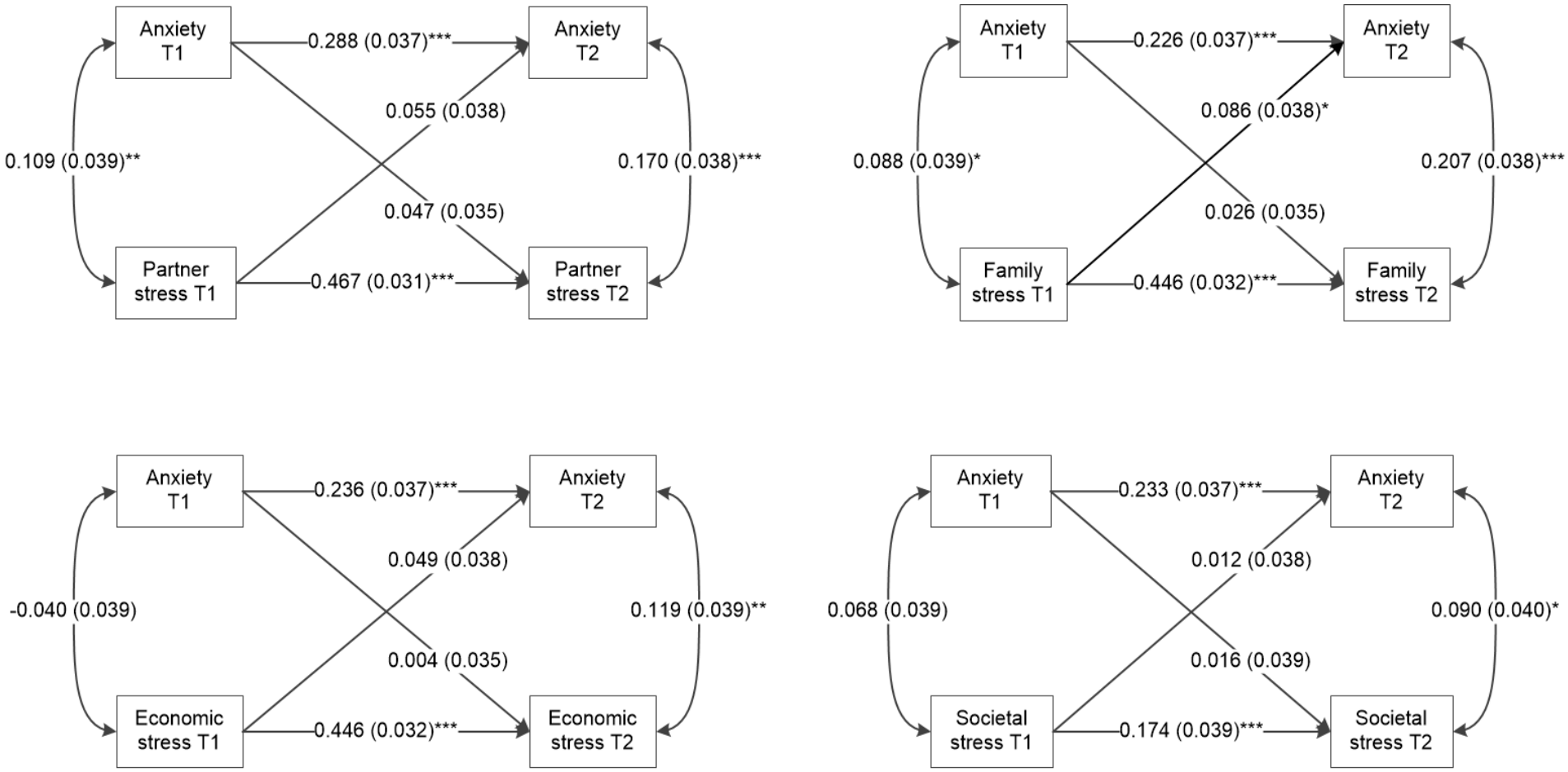

Figure 4.3 Cross-lagged panel model of anxiety and partner, family, economic and societal stress

4.4 Discussion

4.4.1 Summary

Our results show concerning rates of both depression and anxiety in both early and later pregnancy. If depression is present early it tends to persist throughout pregnancy while anxiety increases during pregnancy. We provide strong evidence for a direct effect of depression in early pregnancy on later family stressors, while family stressors in early pregnancy are related to increases in anxiety later in pregnancy.

4.4.2 Prevalence, incidence and timing of onset of depression and anxiety

Our finding that depression (24–28%) and anxiety (14–18%) are high in pregnancy (almost double those seen in HIC) is similar to other research in South Africa and other LMIC (16, 51). A unique contribution of this longitudinal research is that we illustrate for the first time in Africa that risks for both depression and anxiety emerge earlier in the pregnancy than have been previously reported, and that they change over the course of pregnancy. Unlike previous studies, we do not find an association between previous mental illness and depression during pregnancy. We do however find an association between previous mental illness and late onset anxiety (RR 4.82 95% CI [1.5–16.0] p = 0.010) although numbers are a small (n = 7) and confidence intervals are wide.

Most studies of perinatal mental health in Africa to date have been cross-sectional (19) or, if longitudinal, they have tended to measure mental health only once, usually in later pregnancy, with follow up during the postnatal period. For example, one study in South Africa reported on depression rates at more than one time-point in pregnancy, but their published analysis focused only on trajectories from the later time point in pregnancy into the postnatal period without interrogating changes in antenatal depression cases over the course of pregnancy (107). Another study in South Africa has identified the potential risk of early-onset chronic depression during pregnancy (28) however that research was limited by only measuring depression in later pregnancy with retrospective self-report of the timing of onset. This precludes an understanding of the timing of the first emergence of risk, which could inform prevention and treatment opportunities given that early pregnancy onset versus late-onset depression have different etiologies across pregnancy (14).

That depression and anxiety risk is present as early as the first trimester, with approximately 1 in 10 women having comorbid depression and anxiety across

pregnancy warrants attention for two reasons. First, the chronicity of mental health problems has a negative influence on prognosis, so identifying these at the earliest opportunity is beneficial. Second, there are known effects of depression on health-related behaviours such as lower attendance at antenatal care (108), negative perceptions of health care services (Rochat et al., 2006) lower hygiene behaviours (50) and increased risk of substance and alcohol use (109, 110) - all of which can affect the health and wellbeing of both mother and foetus (4).

These effects are not to be underestimated. For example, in HIC studies have shown that depression is associated with obstetric complications (111), preterm delivery and low birth weight (49), while both depression and anxiety are associated with self-harm or suicide (55, 112). Evidence suggests that offspring born to antenatally depressed or anxious mothers are at increased risk of childhood emotional problems and risk of depression in later adolescence, independent of the mother's postnatal mental health (113). Leaving these conditions either undetected or untreated could have substantial long-term consequences.

Our finding that depression and anxiety remain stable or increase during pregnancy highlights the importance of early pregnancy screening and intervention in public health settings. Other studies have shown that antenatal depression and anxiety are both risk factors for postnatal mental health problems (52). We know from the literature that perinatal depression is associated with decreased treatment adherence (including ART), decreased breastfeeding duration and also the negative affect it has on infant bonding (4). In settings such as South Africa, this is particularly concerning given the already high rates of maternal and child morbidity and mortality (114). While screening and interventions for mental health problems may be considered resource-intensive, public health services cannot afford to ignore mental health problems which could potentially worsen health outcomes (even if only indirectly) by lowering maternal health care engagement and adherence (51).

This research contributes to the very limited evidence on the prevalence of anxiety across pregnancy globally. The number of studies which have examined antenatal anxiety (as compared to or together with antenatal depression) is generally limited (39), and is particularly limited in Africa. Of studies of perinatal mental health in Africa, approximately 20 have examined antenatal depression while very few have investigated anxiety (19, 39, 51). Only one other study in South Africa (42) has

specifically examined antenatal anxiety, finding similar rates to this research, but like most studies in Africa to date, uses a cross-sectional design. One longitudinal study of 778 women in Ghana and Cote d'Ivoire (115) found distinct trajectories by examining anxiety in later pregnancy through to the postpartum. That anxiety is largely understudied is concerning because depression and anxiety are known to be highly comorbid, with Stein-Pearson et al. showing that associations attributed to one, might include causes associated with the other, suggesting that while comorbidity is common, disorders are likely distinct and screening and treatment approaches may need to differ (4). Understanding the onset and timing of anxiety is therefore as important as it is for depression, and potentially even more so given the growing evidence from HIC studies of programming effects on children (116).

4.4.3 Stressors and support in the development of depression and anxiety across pregnancy

For all women, pregnancy brings with it many adjustments, which can be stressful for both prospective parents and their families, in particular when pregnancies are either unplanned or unwanted (30). In S1000, a cohort which is largely generalisable to most urbanised and highly transitioned contexts across Africa, stressors were high in early pregnancy and became attenuated during pregnancy, with the exception of partner stress (particularly feeling that your partner makes your life harder), which increased significantly towards the end of pregnancy. While the vast majority of women reported high levels of both practical and emotional support, the impact of the absence of support, and the importance of the potentially negative perceptions of support by women with depression, were clearly demonstrated in this study.

In all the cross-lagged models examining the direction of effect between depression and stressors across the pregnancy, we see evidence of a direct effect of depression scores in *early* pregnancy to reporting of stress in *later* pregnancy. This effect from early depression to later stress is strongest for family stress in later pregnancy. This may indicate two possibilities: the depression symptoms (including low mood, irritability, low of interest) may lead to a change in behaviours (with pregnant women becoming more sensitive to criticism, irritable and potentially withdrawing from relationships), making family interactions difficult and strained; or the depression leads to a more pessimistic outlook by the pregnant women on family relationships, which she then reports as higher family stress (27) . Family stress was also associated with a twofold increase in risk for persistent anxiety, and an increased risk

of early pregnancy anxiety. When examining the direction of this effect between anxiety and family stress across the pregnancy, we show that family stress in early pregnancy predicts an increase in anxiety scores in later pregnancy. This is plausible in terms of both the literature, and pragmatically, as without family support pregnancies are likely highly distressing and this may become heighted as the birth of the child becomes more imminent.

Importantly, we find that these stressors are likely modifiable because support has a protective effect for most women, particularly depressed women, in this cohort and in the literature (15). Traditional African families are large and consist of many extended families members living together and taking care of one another (117). The support offered by these extended families serves as a buffer for high rates of stress (118). It is possible that in populations such as Soweto, the nature of urbanisation separates women from their extended family. We see in this cohort that about half of women were living in a household with a maximum of 3 people, including themselves. It is possible that family stress is experienced in an exaggerated way in this cohort because women are not benefitting from the support offered by larger extended families.

Like many studies, we find that a stressed or poor quality partner relationship and an absence of partner support is associated with poorer mental health (39). We show that the perception of a difficult relationship or an unsupportive partner increases risk, which is greatest in the group of women with persistent depression. We also show that being able to speak to or confide in one's partner is associated with decreased risk of persistent depression. This suggests that supportive partners are central to a woman's mental health in pregnancy. While we also show that partner stress early in the pregnancy is associated with later depression, it is noteworthy that we also demonstrate that depression early in the pregnancy is linked to later partnership stress, highlighting the reciprocal nature of both. Since partner support is shown to be important for a variety of pregnancy and child outcomes, this research highlights the importance of attending to the partner relationship in the interests of good pregnancy care and better mental health. It suggests that mental health problems such as depression during pregnancy, could potentially be instrumental in the development of partner stress and marital conflict, which could disrupt the benefits of partner support (119).

Further research should consider including both pregnant women and their partners accounts of the presence or absence of partnership stress, difficulties and support during pregnancy. This is important because at least some evidence has suggested that fathers are also vulnerable to perinatal depression and that this vulnerability is heighted in the presence of maternal depression, with concerning consequences for parenting capacities (120). In African settings pregnancy services are highly feminised and there are barriers to partner engagement, including cultural practices limiting the involvement of fathers when children are born out of wedlock (121). Increased public awareness of and greater acknowledgement of the contribution partners may make to healthier happier pregnancies is needed (122).

4.4.4 Limitations

Although some women were excluded because they did not have data at both time points, sensitivity analysis found little to no differences in baseline characteristics between those included and excluded from this analysis. While the two mental health scales used (EPDS and STAI) are well validated and widely used, they are not diagnostic measures of depression or anxiety. It would be important to interrogate who provides women with practical and emotional support, as this would determine who interventions to reduce the risk for depression and anxiety.

4.4.5 Conclusion

To the best of our knowledge, this is the first study of its kind to investigate the timing of onset and duration of both probable depression and anxiety during pregnancy, their comorbidity and to examine the potentially modifiable mechanisms involved in their onset and persistence.

Chapter 5 : Thoughts of self-harm in early and late pregnancy in urban South Africa: Investigating prevalence, predictors and screening options[3]

[3] Redinger S, Pearson RM, Houle B, Norris SA, Rochat T. Thoughts of self-harm in early and late pregnancy in urban South Africa: Investigating prevalence, predictors and screening options S Afr Med J. 2021;111(7):627-34.doi: 10.7196/SAMJ.2021.v111i7.15058

5.1 Introduction

Young women and adolescent girls are particularly vulnerable to self-harm, including in sub-Saharan Africa (53). While many of these women might be mothers, or at least of child-bearing age, there is very little research on thoughts of self-harm (TSH) during the perinatal period (123). Most research has been cross-sectional and limited to the postnatal period (123). The few studies in South Africa investigating TSH and suicidal ideation during pregnancy have found prevalence's of between 12-39%, which is up to double rates found in high income countries (HIC) (54). South Africa also has high rates of antenatal mood disorders (101, 124), which have been shown to be a common risk factor for TSH. (54, 55).

Despite evidence of risk during pregnancy, there are few routine screening programmes to identify TSH or suicidal ideation for pregnant women in low and middle income countries (LMIC). Both TSH and suicidal ideation are known antecedents of suicide attempts (125), suggesting that early detection and prevention of TSH would have significant public health potential. While the justification for early detection may be compelling, resistance to the introduction of time-intensive screening procedures, in an already over-burdened public health system, is likely to be high. Developing our understanding of how to efficiently detect and evaluate risk for TSH is central to reducing barriers to early detection, and to focus limited prevention efforts where and when they are most needed.

We use longitudinal data from an urban cohort of pregnant women in Soweto, South Africa to investigate TSH in both early and later pregnancy. We report on prevalence, onset and duration of TSH, exploring both individual and contextual factors that are associated with TSH. We investigate the relationship between TSH, depression and anxiety, and make recommendations for approaches to, and timing of, screening efforts in low resource settings.

5.2 Methods

5.2.1 Setting

The study was nested within a large pregnancy cohort study – the Soweto First 1000 Days Study (S1000) – based at the Developmental Pathways for Health Research Unit (DPHRU) in Johannesburg, South Africa. The overall aim of the S1000 cohort was to investigate the associations between multiple maternal factors during pregnancy (including health, nutrition) and fetal and infant outcomes.

5.2.2 Participants

Pregnant women were enrolled into the study from the Fetal Medicine Unit at Chris Hani Baragwanath Academic Hospital (CHBAH) between 2014-2016. Inclusion criteria for S1000 were as follows: resident of Soweto, <20 weeks gestational age at recruitment, non-epileptic, non-diabetic, 18 years or older and pregnant with a singleton, naturally conceived pregnancy. Women were followed through pregnancy and up until their child's second birthday, with data being collected at 14 timepoints during this period. This study reports on data collected at two timepoints during the pregnancy period only (T1: first trimester, T2: late second trimester). These timepoints were study-specific and not necessarily linked to routine antenatal appointments.

Any participant reporting TSH during an assessment was referred to a senior professional nurse (with mental health training) at DPHRU for counselling. This nurse also facilitated a referral to mental health support services at CHBAH, and made follow-up calls to ensure that the participant was receiving these services.

All women provided written informed consent prior to their inclusion in the pregnancy component of the study (Soweto Fetal Growth Study; SFGS). Ethical approval was obtained from the University of the Witwatersrand's Research Ethics Committee (Medical) for data collection [M120524] and data analysis [M160670] [M180949].

5.2.3 Measures

Probable depression, anxiety and TSH were collected at both timepoints in pregnancy, using validated psychometric scales.

<u>Depression:</u>

The Edinburgh Postnatal Depression Scale (EPDS) (126) is a well validated 10-item screening tool for perinatal depression which has shown good internal consistency

and scale reliability in this cohort (Cronbach 0.80) and in other South African studies (28, 79). Items are scored on a severity scale (0 to 3) and summed for a total score of 30.

Anxiety

The State Anxiety Inventory Short Form (STAI-6) is a 6-item version of the 20-item Spielberger State-Trait Anxiety Inventory Index, which has shown good internal consistency reliability and validity when correlated with the original scale (82, 105). Item are scored on a severity scale (1-4) and summed for a total score of 24.

Thoughts of self-harm

Using an approach common in the literature (127), reports of TSH were identified using Item 10 of the EPDS which states: "The thought of harming myself has occurred to me". Respondents self-reported TSH in the preceding 7 days on a Likert scale scoring 0 (never), 1 (hardly ever), 2 (sometimes) or 3 (quite often).

5.2.4 Data analysis

Analysis was performed in StataSE version 15 (86) and MPlus version 8.3 (106).

Consistent with previous analyses of this cohort (101, 128), the baseline covariates included in this analysis were selected a priori based on theoretical evidence (56, 57, 129). Baseline individual and contextual covariates included maternal age, relationship status, pregnancy intention, education, asset ownership, health status, social support (practical and emotional) and social stressors (partner, family, economic and societal). Differences between baseline characteristics of women with and without TSH were determined using non-parametric tests (Chi-Square, Wilcoxon rank-sum).

Probable depression was identified using a cut-off of ≥13/30 on the EPDS (80). Using the same approach as authors of the original full length STAI (>40/80) (82), probable anxiety was determined using the midpoint (≥12/24) of the short form scale as a cut-off.

The TSH outcome variable for use in the logistic regressions and MPlus models was constructed from EPDS Item 10. Responses of “Never” and “Hardly ever” were coded as (0) *‘no thoughts of self-harm’* and responses of “Sometimes” and “Yes, quite often” as (1) ‘*thoughts of self-harm present’.* This dichotomous variable was used to

calculate the presence or absence (prevalence) at each timepoint. Additionally, a variable describing the presence or absence of TSH across the pregnancy was created: (0) No TSH at any point during pregnancy *'thoughts of self-harm never'*; (1) TSH at either T1 or T2, or both T1 and T2 *'thoughts of self-harm ever*'.

Logistic regression was used to determine the strength of associations between TSH 'ever' and baseline covariates (including T1 depression and anxiety) – with women who *'never'* reported TSH as the reference group.

To explore the relationship between TSH and symptoms of depression and anxiety, we used confirmatory factor analysis (CFA) in MPlus to develop latent factors and logistic regression in STATA to explore associations. First, the individual items of the EPDS and the STAI scales were organised into specific depression and anxiety factors. Then, given the strong evidence of depression and anxiety being highly co-morbid and sharing characteristics (128), we also created a shared depression/anxiety factor. In creating the shared factor, each item of both the EPDS and STAI contributed variance to the unique depression and anxiety factors previously created as well as contributing to the shared depression/anxiety factor. We then used the three factors to test model fit for the individual depression, anxiety factors and the shared depression/anxiety factor. For the CFA models, model fit was evaluated using root mean square error of approximation (RMSEA), comparative fit index (CFI) and Tucker–Lewis index (TLI). RMSEA is an absolute measure of fit adjusted for model complexity (values closer to zero indicate good fit), and we used an upper limit of <0.06 to indicate good fit. As CFI and TLI are measures of fit compared to the null with no correlations, when interpreting these indices we used the values >0.90 to indicate good fit (130).

We explored the relationship between these factors and later TSH in a bifactor model using the depression, anxiety and shared factors as independent variables and TSH 'ever' as a dependent variable. Because CFA latent variables use individual items to contribute to variance, and given that the TSH variable was created using EPDS 10, for this particular analysis the depression factor was created without using item 10. We could not explore the association between early TSH (as an independent variable) on later depression or anxiety as dependent variables in MPlus because TSH was created as a dichotomous variable and therefore could not be used as an independent variable in MPlus. Instead, to explore the association between reporting

early TSH (T1) and later TSH and mental health problems (TSH, depression or anxiety at T2), we used logistic regression analysis in STATA.

5.3 Results

5.3.1 Description of sample

Of the 1,055 enrolled women, 649 had psychological data at both timepoints and are included in this analysis (Figure 5.1). Women who did not have complete psychological data at both timepoints were excluded from the analysis. When comparing prevalence of TSH between women with data only at T1 or T2 with those who had data at both timepoints, we see no significant difference in rates using Chi-squared tests. At T1, rates of TSH among women included were 12.5% while excluded women were 11.4% (p=0.646). At T2, while those excluded had lower rates of TSH (7.0%) compared to those included (11.6%) this was not significant (p=0.297). Previous sensitivity analysis (128)also demonstrated little to no differences in sociodemographic variables (a difference of 0.3 on an asset score out of 11) between those with complete data and those with incomplete data (i.e., data at only one timepoint). Sample characteristics are shown in Table 5.1. Women with TSH in pregnancy tended to be younger, single, pregnant with their first child, and had a lower asset score and fewer years of education.

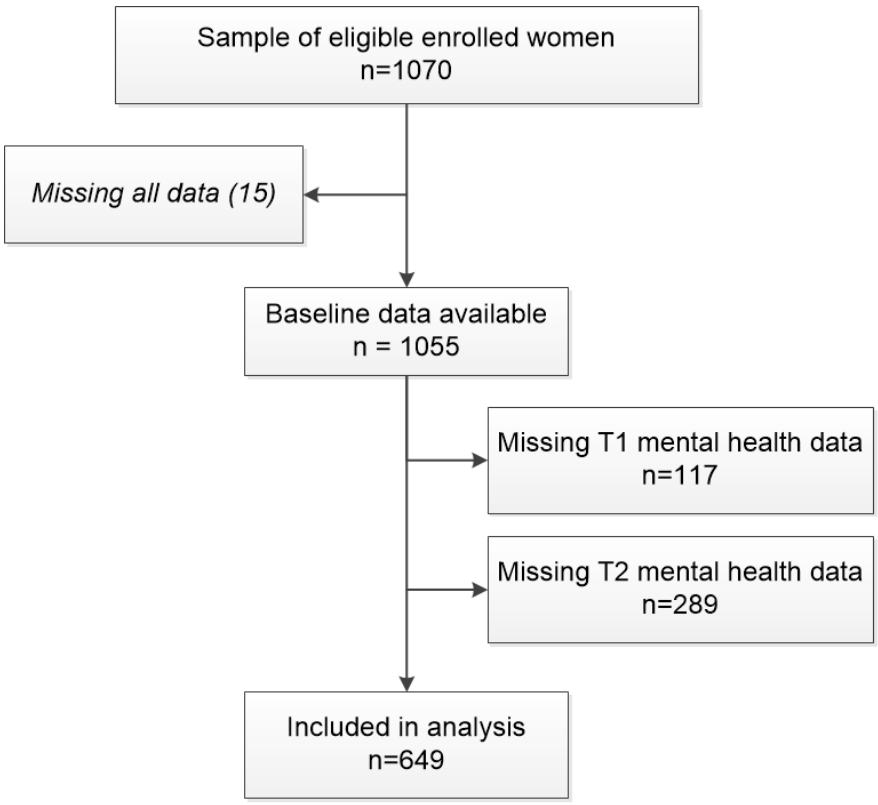

Figure 5.1 Consort diagram of participating women included in the analytic dataset

Table 5.1 Sample characteristics of women by presence of thoughts of self-harm (n=649)

	Total (n=649)			No TSH (n=531)			TSH in pregnancy (n=118)			
	n	%	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)	p-value
Age			29.6 (5.9)			30.0 (5.8)			27.9 (5.5)	<0.001
Education										
None/ up to Gr 12	464	72.3		371	70.7		93	80.2		0.036
Post-matric	178	27.7		154	29.3		23	19.8		
missing	7			5			2			
Marital status										
single	407	62.8		322	60.8		84	71.8		0.026
married/cohabiting	241	37.2		208	39.2		33	28.2		
missing	1			1			1			
Household: no. people										
≤3	307	48.9		257	49.9		49	43.8		0.230
≥4	321	51.1		258	50.1		63	56.3		
Missing	21			15			6			
Household: no. <5 years										
No children under 5 yrs	421	66.2		349	67.0		71	62.3		0.329
Children under 5 yrs	215	33.8		172	33.0		43	37.7		
Missing	13									
Asset score			5.5 (1.5)			5.6 (1.4)			5.3 (1.6)	0.020
Parity										
1st pregnancy	174	27.1		129	24.7		45	38.1		0.003
2nd+ pregnancy	468	72.9		394	75.3		73	61.9		
missing	7			7			0			
Pregnancy intention										
unplanned pregnancy	333	52.3		266	51.0		66	57.9		0.185
planned	304	47.7		256	49.0		48	42.1		
missing	*12*			*8*			*4*			
Smoked (last 3 months)										
No	592	91.2		488	92.1		103	87.3		0.095
Yes	57	8.8		42	7.9		15	12.7		
Missing	0			0			0			
Alcohol use (this pregnancy)										
No alcohol use	546	88.1		450	88.4		95	86.4		0.544
Weekly alcohol use	74	11.9		59	11.6		15	13.6		
Missing	29			21			8			
Mental illness (previous)										
No	632	97.4		519	97.9		112	94.9		0.064
Yes	17	2.6		11	2.1		6	5.1		
Missing	0			0			0			
HIV status										
HIV negative	444	70.3		369	71.2		74	65.5		0.221
HIV positive	188	29.7		149	28.8		39	34.5		
missing	17			12			5			

5.3.2 Prevalence of thoughts of self-harm

Prevalence of TSH was slightly higher in early pregnancy compared to later in pregnancy. A total of 118 (18.2%) had TSH at some stage during pregnancy (either T1 or T2, or both T1 and T2), while 5.9% (n=39) of women reported TSH at both timepoints. Of the women who had TSH ever, 100 (84.7%) had TSH alongside either depression or anxiety or both, while 18 (15.3%) women had TSH without either depression or anxiety being present.

5.3.3 Multivariate logistic regression model

In the multivariate logistic regression model (Table 5.2), depression (aOR 4.81 95%CI [2.7-8.6] p<0.001), anxiety (aOR 2.72 95%CI [1.5-5.1] p<0.001) and a history of mental illness (aOR 4.17 95% CI [1.3-13.7] p=0.020) prior to pregnancy were significantly associated with higher odds of TSH at some point in the pregnancy. Those reporting marital stress had higher odds of reporting TSH (aOR 1.74 95%CI [1.0 - 3.0] p=0.040), while having practical support was associated with lowered odds of TSH (aOR 0.43 95%CI [0.2-1.0] p=0.040).

5.3.4 Confirmatory Factor Analysis

Using the observed depression and anxiety scale items, both a unifactor and a bifactor model were fitted in MPlus to examine the existence of a general latent factor for depression and anxiety (Figure 5.2). The unifactor models at both timepoints had poor fit - T1: RMSEA (0.071 90% CI 0.065 - 0.078); CFI (0.838) and TFI (0.812); T2: RMSEA (0.081 90% CI 0.075 - 0.088); CFI (0.81) and TFI (0.78). At both timepoints, the bifactor model with the general shared factor had the best model fit – at T1: RMSEA (0.056 90% CI 0.048 - 0.063); CFI (0.92) and TFI (0.89) and T2: RMSEA (0.066 90% CI 0.058 - 0.073); CFI (0.90) and TFI (0.86).

When examining the association of early (T1) depression, anxiety and the shared factor on later TSH, the largest association was with the shared factor (standardised estimate 0.468, SE 0.065, p<0.001). There was no association between the unique anxiety factor and later TSH (standardised estimate 0.100, SE 0.066, p=0.129), however depression alone was associated with TSH (standardised estimate 0.393, SE 0.071, p<0.001).

Table 5.2 Univariate and multivariate logistic regression models of thoughts of self-harm during pregnancy (n=649)

	Univariate	Multivariate
	OR [95%CI] p	**aOR [95%CI] p**
Age[a]	0.94 [0.90-0.97] 0.001	0.95 [0.9-1.0] 0.080
Education		
None/ up to Gr 12	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Post-matric	0.60 [0.36-0.98] 0.040	0.74 [0.4-1.5] 0.390
Marital status		
single	1.00 [1.0-1.0]	1.00 [1.0-1.0]
married/cohabiting	0.61 [0.4-0.9] 0.026	0.95 [0.5-1.8] 0.870
Household: total number of people		
≤3	1.00 [1.0-1.0]	1.00 [1.0-1.0]
≥4	1.28 [0.9-1.9] 0.238	1.21 [0.7-2.2] 0.530
Household: people under 5 years		
No children under 5 years	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Children under 5 years	1.23 [0.8-1.9] 0.337	1.07 [0.6-2.0] 0.820
Asset score[a.b]	0.87 [0.8-1.0] 0.030	0.89 [0.7-1.1] 0.280
Parity		
1st pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]
2nd+ pregnancy	0.53 [0.4-0.8] 0.003	1.01 [0.5-1.9] 0.990
Pregnancy intention		
unplanned pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]
planned	0.76 [0.5-1.1] 0.180	1.16 [0.7-2.1] 0.600
Smoked (last 3 months)		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1.69 [0.9-3.2] 0.100	0.85 [0.3-2.4] 0.760
Alcohol use (this pregnancy)		
No alcohol use	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Weekly alcohol use	1.03 [0.9-1.2] 0.736	1.08 [0.9-1.4] 0.500
HIV status		
HIV negative	1.00 [1.0-1.0]	1.00 [1.0-1.0]
HIV positive	1.31 [0.9-2.0] 0.227	1.16 [0.6-2.1] 0.630
History of mental illness (previous)		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	2.53 [0.9-7.0] 0.073	4.17 [1.3-13.7] 0.020
Depression (current)		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]

Yes	6.00 [3.9-9.2] <0.001	4.81 [2.7-8.6] <0.001
Anxiety (current)		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	3.45 [2.1-5.5] <0.001	2.72 [1.5-5.1] <0.001
Antenatal stressors[a]		
Marital stress	2.48 [1.7-3.6] <0.001	1.74 [1.0-3.0] 0.040
Family stress	1.35 [1.07-1.7] 0.012	0.89 [0.6-1.3] 0.510
Economic stress	1.12 [0.9-1.4] 0.270	0.88 [0.6-1.2] 0.400
Societal stress	1.07 [0.7-1.7] 0.790	0.55 [0.3-1.2] 0.120
Has practical support		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.24 [0.1-0.4] <0.001	0.43 [0.2-1.0] 0.040
Has confidante		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.40 [0.2-0.8] 0.011	0.82 [0.3-2.3] 0.700
Partner is confidante		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.40 [0.2-0.8] 0.014	0.67 [0.3-1.8] 0.420
Clinic staff are friendly		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.46 [0.3-0.9] 0.015	0.93 [0.4-2.4] 0.890
Partner makes life harder		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	2.02 [1.4-3.0] 0.001	1.33 [0.7-2.4] 0.350
Has friend with baby		
No or sees irregularly	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes. sees regularly	0.97 [0.6-1.5] 0.907	1.08 [0.6-1.9] 0.780

[a] Age. asset score and marital stressors were used as continuous variables in the analysis

[b] Asset score ranges from 0 to 11 and is calculated by adding the items in the household including. electricity. radio. television. refrigerator. cell phone. personal computer. farm animals. agricultural land. bicycle. motorcycle/scooter and vehicle.

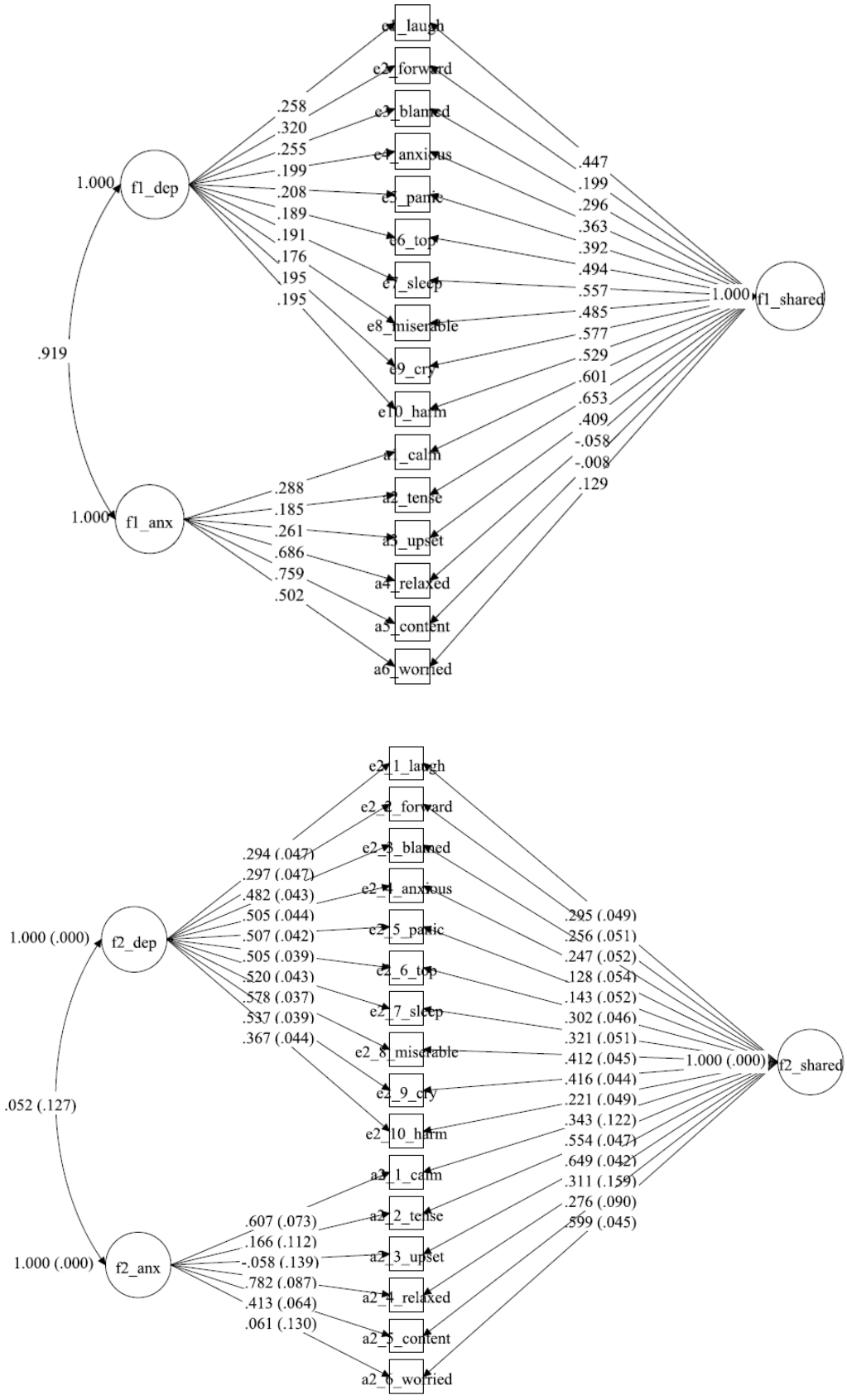

Figure 5.2 Bifactor model of depression, anxiety and a general factor at T1 and T2

f1_dep: depression factor at T1; f1_anx: anxiety factor at T1; f1_shared: shared depression/anxiety factor at T1. f2_dep: depression factor at T2; f2_anx: anxiety factor at T2;

Table 5.3 shows the EPDS and STAI items contributing the highest variance to the shared factor at each timepoint. TSH was one of these items at T1, but not at T2. Items common to both timepoints were EPDS item 9 (I have been so unhappy that I have been crying) and STAI items 1 (I feel calm, reversed scored) and 2 (I feel tense).

In terms of the impact of early TSH on later TSH, depression and anxiety, TSH at T1 was strongly associated with TSH at T2 (OR 12.7 95% CI [7.3-22.0] p<0.001), however this effect was attenuated when controlling for depression at T1 (aOR 9.9 95% CI [5.3-18.2] p<0.001). Early TSH was not associated with later depression (aOR 1.33 95% CI [0.7-2.5] p=0.357) or anxiety (aOR 1.66 95%CI [0.9-3.0] p=0.095) when controlling for later TSH.

Table 5.3 Items of the EPDS and STAI contributing the highest variance onto the shared depression/anxiety factor

Timepoint 1		**Timepoint 2**	
		EPDS 8	I have felt sad or miserable
EPDS 9	I have been so unhappy that I have been crying	**EPDS 9**	I have been so unhappy that I have been crying
EPDS 10	The thought of harming myself has occurred to me		
STAI 1	I don't feel calm	**STAI 1**	I don't feel calm
STAI 2	I feel tense	**STAI 2**	I feel tense
		STAI 6	I feel worried

5.4 Discussion

In this study we find a prevalence of TSH of 18%, which is similar to other South African studies, and confirms that TSH are a significant public health concern. To the best of our knowledge, this is the first study in South Africa to demonstrate that TSH are present as early as the first trimester of pregnancy, and that prevalence is slightly higher in early pregnancy as compared to later pregnancy. Similar to other studies, we find TSH are frequently reported in the context of concurrent depression, and that a history of mental illness is strongly associated with TSH during pregnancy (24, 57, 107), TSH are more likely amongst women with marital stress, and less likely amongst those with good support. Lastly, we show that a combination of scale items on depressive and anxious symptoms best identifies women who endorse the TSH item in later pregnancy.

While suicidal risk amongst pregnant women is still largely under-researched in South Africa, there is growing evidence that risk for TSH is substantial, potentially double that reported in most HIC studies (129, 131). Previously, cross-sectional studies in urban South Africa reported rates of 12, 18 and 19.8% (24, 57, 107), while in rural populations (with concurrent HIV) much higher prevalence rates of up to 39% have been reported (56, 132). Using repeated measures of TSH, depression and anxiety, we are able to demonstrate that TSH start early, remain high in pregnancy, and that early TSH increases the odds of later TSH, especially in the context of depression. Previous cross-sectional research reporting only on TSH in later pregnancy may have underestimated the extent of antenatal risk.

The public health justification for regular, routine mental health screening starting early in pregnancy in South Africa is therefore compelling, and ignoring the early warning signals could have far reaching consequences. Beyond the risk of TSH alone, is the risk of these progressing to suicide attempts, or in rare but tragic cases, completed suicide. A nationally representative study of South African adults has shown that half of suicide attempts occur within a year of the onset of reporting suicide ideation (133). Furthermore, suicide is a leading cause of death during the first postnatal year (3), and has devastating effects not only for the expectant or new mother, her fetus or newborn, but also her other children and family (134).

Regardless of this strong justification for supporting early screening, finding a balance between the need to screen and detect while limiting public health burden, will likely be key to the acceptability and feasibility of increased screening in public health clinical settings. Some research in South Africa has already advocated for ultra-short screening in primary healthcare settings (135) While we provide support for those calls, our research suggests that focusing only on depressive screening items may have limitations. The results of the logistic regression models show that depression and anxiety are both strongly associated with later TSH. In the bifactor models we show that the shared factor (symptoms of both depression and anxiety) had the strongest association with TSH in later pregnancy. This suggests that it is a combination of screening questions about both depressive and anxious symptoms which might best identify or predict later reports of TSH.

Enquiring, from the first antenatal contact whether a pregnant women has been feeling tense and unable to calm herself, feeling so unhappy that she has been

crying or has had thoughts of harming herself, may provide health care practitioners a simple and approachable way to enquiring about mental health, which is not overly technical. These short, gentle enquiries about emotional coping, alongside queries about support (both marital and otherwise) may help to reduce the stigma associated with mental health problems. It may also encourage greater disclosure by patients in healthcare provider interactions, which in turn could facilitate timely, efficient and targeted referrals. The potential to mitigate risk for at-risk individuals surely far outweighs the additional time burden of introducing these mental health related screening questions during antenatal consultations.

Identification alone has no real benefit at a population level when treatment is not available, and therefore finding cost-efficient ways to not only identify, but also respond, is critical. In this cohort all women reporting TSH at T1 received at least one study-supported counselling session, and were referred into routine mental health care services. Despite this, a significant proportion had a similar response at T2, with rates of TSH increasing in later pregnancy suggesting that the intensity and content of existing interventions may need to be enhanced to respond to this high risk population. When controlling for depression and anxiety, women reporting marital stress were almost twice as likely to have TSH as those without, and having practical support halved the odds of reporting TSH. Including partner and family-based support in mental health care services and interventions could enhance existing intervention approaches and highlights the important role a multidisciplinary team (including social workers and psychologists) can play in delivering pregnancy care.

5.5 Strengths and weaknesses

The strengths of this study include its longitudinal design and that it measures both depression and anxiety, alongside rich contextual data. Limitations include that while we report on TSH during pregnancy, we do not have any additional information on the extent of suicidal ideation, for example whether women have intent and plans, or any history of suicidal attempts. However, in another study in South Africa, item 10 on the EPDS “the thought of harming myself has occurred to me” was found to have good sensitivity of 77% (CI 57 - 89) and excellent specificity of 92% (CI 83 - 96) for detecting suicide ideation when compared to a clinical interview (Rochat 2013). Additionally, in this study the approach to defining TSH was more conservative than previous South African studies, some of which included a response of “hardly ever” as indicating TSH (Rodriguez et al., 2018a; Rodriguez et al., 2018b), suggesting this

research has provided a sound estimate of potential risk. Even though a third of women of the full cohort did not have mental health data at both timepoints, large numbers of women were retained in the study at timepoint 2, providing us with sufficient data to establish that it was unlikely that systematic biased was introduced by having missing data. There is growing evidence of the negative impact of internet and social media use on self-harm and suicidal behaviours (136). Currently, most of this research is focused on children and adolescents, including in South Africa (137). While we did not measure the impact of internet and social media use on TSH in this study, we feel that it should be explored in future studies of mental health in South Africa.

5.6 Conclusion

Given that TSH is a robust predictor for attempted suicide (54), these findings call attention to the need for early detection to identify the small subset of women requiring urgent evaluation and care, as early as possible in pregnancy. In low resource public health settings, the reporting of TSH by patients immediately places a responsibility on healthcare providers to ensure the safety and care of the patient. In this regard the services of public health psychiatric nurses, psychologists and social workers play a key role, as do interventions delivered by lay counsellors or community health care workers, and a wide range of non-governmental services positioned to respond to mental health crises. Healthcare workers in perinatal settings could easily be trained in approachable, effective screening methods, but emergency response and referral protocols need to be developed within their institutions or communities to assist with case management. How this might be operationalised in tertiary versus decentralised primary health care institutions, where such human resources may be scarce, is less understood and warrants further investigation. Importantly, what this research does demonstrate is that not measuring or identifying risk of self-harm does not invalidate the likely presence of TSH, and that taking a ‘don’t ask, don’t tell’ approach not only raises an ethical dilemma for healthcare practitioners, but may further stigmatise TSH amongst the 2 out of 10 pregnant women at high risk in their patient population.

SECTION 3: INTEGRATED DISCUSSION AND CONCLUSION

Chapter 6 : Integrated discussion

6.1 Introduction

As demonstrated throughout this thesis, in South Africa and in Africa more broadly the majority of perinatal mental health studies have been cross-sectional (19). Those studies which do have repeated measures of mental health have largely focused on identifying trajectories (particularly of depression), from late pregnancy through to the postnatal period (38). This provides a limited understanding of how to approach screening, treatment and prevention in South Africa and other similar contexts (14, 28, 107).

For the most part, the findings in this study on antenatal depression align with much of what is already known internationally about the prevalence and timing of antenatal depression (5), and its strong association with thoughts of self-harm (123). This study does, however, illustrate that risk starts much earlier than most studies currently report (15). The findings on antenatal anxiety are more unique and contribute to the existing international literature, since this is one of only three studies in South Africa to examine antenatal anxiety, and to my knowledge, the first to do so using longitudinal data.

This chapter will explore the epidemiological profile of each of these disorders, how they relate to each other, and highlight implications for screening and treatment approaches. The chapter will focus first on high-intensity treatment modalities for high-risk individuals, before exploring the opportunities for lower-intensity, family-centred approaches to intervention. I will also discuss the important contributions partner and family support can make in addressing lower levels of risk and promoting mental health for both pregnant women and their partners.

6.2 Summary of study findings

An overview of study findings per objective is provided in Table 6.1.

Table 6.1 Summary of research findings per study objective

Thesis Chapter	Study Objective	Key findings	Conclusion
Chapter 3 (Paper 1)	To determine the prevalence of and factors associated with depression and anxiety in early pregnancy.	Prevalence of antenatal depression was 27% (95% CI 24.2-29.8) and anxiety 15.2% (95% CI 12.9-17.5), while 34.4% of women had either depression and anxiety, and 7.3% had both. Factors associated with antenatal depression and anxiety were predominantly relationship- and family-centred. Women who perceived that their partner made life harder for them had threefold increased odds for depression (OR 3.33 95% CI [2.28-4.85] p<0.001) while those with family stressors had almost double the odds for depression (OR 1.78 95% CI [1.22-2.59] p=0.003) and anxiety (OR 1.75 95% CI [1.44-2.69] p=0.0011).	As hypothesised, in this study I conclude that both depression and anxiety are common in pregnancy, with a third of women experiencing one or both disorders. I also confirm the hypothesis that risk for depression and anxiety starts earlier in pregnancy than previously reported.
Chapter 4 (Paper 2)	Develop a better understanding of the prevalence, onset and duration of both depression and anxiety in	Rates of depression decreased slightly across pregnancy (early pregnancy: 27%; later pregnancy: 25%), while rates of anxiety increased (early pregnancy: 15%; later pregnancy: 17%). Pregnant women reporting ‘my partner made my life harder’	As hypothesised, this study demonstrates that partner and family related support and stress are central to both depression and anxiety, and contribute to their persistence during

	pregnancy and the factors involved in their emergence or persistence across pregnancy.	had higher risk ratios for persistent depression (RR 5.92 95% CI [3.0-11.8] p<0.001); family stress increased risk for persistent anxiety (RR 1.71 95% CI [1.1-2.7] p=0.027). There is evidence of a direct effect of early depressive symptoms (T1) on later family stress (T2); and early family stress (T1) on later anxious symptoms (T2).	pregnancy.
Chapter 5 (Paper 3)	To determine the extent to which women report TSH during pregnancy, and how this relates to depression, anxiety and other stress and protective factors	Prevalence of TSH was slightly higher in early pregnancy (12.5%) than later pregnancy (11.6%), with 18% of women reporting TSH at either/both timepoints. In multivariate logistic regression, TSH was associated with a history of mental illness (aOR 4.17 95% CI [1.3-13.7] p=0.020); concurrent depression (aOR 4.81 95%CI [2.7-8.6] p<0.001); marital stress (aOR 1.74 95%CI [1.0 - 3.0] p=0.040), while practical support (aOR 0.43 95%CI [0.2-1.0] p=0.040) was associated with lowered risk for TSH. Logistic regressions showed that early depression was a strong predictor of later reports of TSH. Bifactor analysis examining depression and anxiety scales showed that the TSH item	This study confirms in part, the hypothesis that TSH are common in pregnancy, although we show that they are associated with depression as a single construct, but not anxiety. Although, TSH are associated strongly with a shared depression and anxiety factor.

		contributed the highest variance to a shared depression and anxiety factor in early pregnancy. An examination of items which best predicted TSH however included not only items related to depression, but also featured strongly items about panic, worry and feeling tense.	

6.3 The epidemiology of antenatal depression and anxiety

The epidemiological profile of women in this sample included that most had completed high school education, were between 25-34 years old, and had at least two children. Many women presented with characteristics which are known to elevate risk of perinatal mental health disorders in the literature, including that two thirds were single or separated from their partners, half reported an unplanned pregnancy, and a third were HIV positive. Approximately a quarter of these women had specific risk factors for mental health problems, including current smoking, alcohol use, a history of mental illness and high levels of relationship and societal stress. The characteristics of this sample were not dissimilar to those reported in other studies of perinatal mental health in South Africa, and align closely to what is known about women of childbearing age in South Africa more broadly (63, 124).

6.3.1 Prevalence of antenatal depression

In this urban sample, the risk for antenatal depression starts as early as the first trimester and, while it appears to remain largely stable, it does decrease by a few percentage points from 27 to 25% by the transition from second into third trimester (between 24 to 26 weeks gestation). This may in part reflect a positive adjustment to some of the earlier stressors present at the start of pregnancy, in particular in the case of unplanned pregnancy (138). The decrease in rates over time may also reflect higher levels of support from increased contact with antenatal services, or from support networks as the pregnancy became more evident (12). Evidence on antenatal depression in South Africa prior to this study had demonstrated a prevalence of between 14 to 40% dependent on the risk profile of enrolled participants. Studies with women with HIV for example, or those experiencing high levels of domestic violence or socio-economic adversity often reported higher prevalence, with some studies reporting rates of up to 50% (27, 28, 36, 37).

In the global literature, where first trimester measures are more common, there are varying reports of when prevalence of depression is highest during pregnancy. Systematic reviews have reported that prevalence increases over pregnancy and a meta-analysis of 21 studies found prevalence rates of 7.4%, 12.8% and 12.0% for the first, second, and third trimesters respectively (1). The authors of this meta-analysis noted, however, that given the limited number of studies collecting first trimester mental health data, the rates for the first trimester were based on fewer studies, and therefore had a smaller sample compared to later trimesters.

Figure 6.1 illustrates an important finding of this research – that in the absence of measures in the first trimester there has long been an assumption that risk escalates in mid to late pregnancy, when in fact this study suggests it may be more stable across pregnancy. This presents tremendous opportunities for prevention, given that early identification and treatment of depression may reduce its burden in later pregnancy and into the postnatal period. Early contacts with healthcare services around the identification of the pregnancy around 8 to 13 weeks therefore present an ideal opportunity to increase identification efforts.

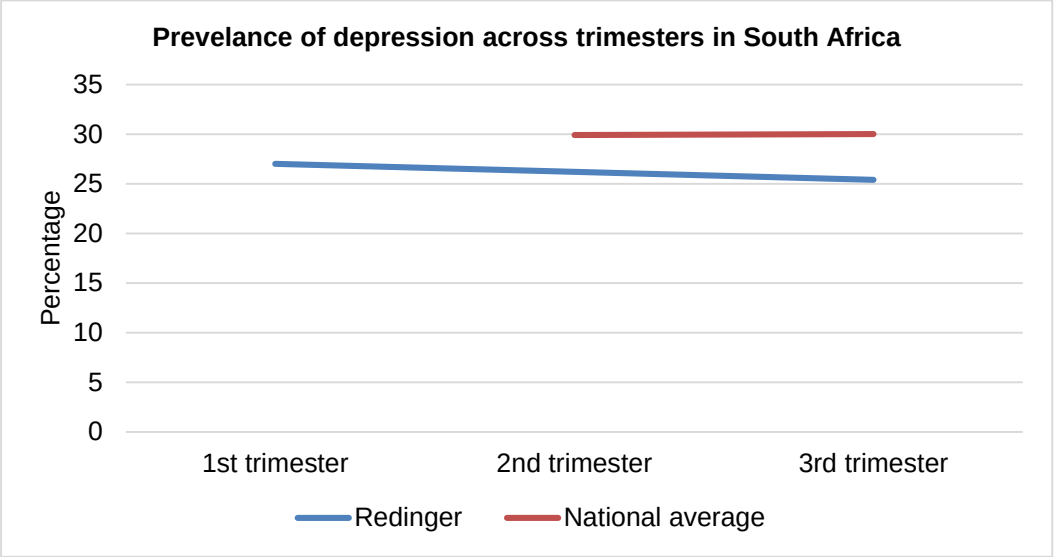

Figure 6.1 Graph showing prevalence of depression as found in South African studies to date

6.3.2 Prevalence of antenatal anxiety

Antenatal anxiety, on the other hand, follows an inverse pattern compared to depression in that it increased by a few percentage points from 14 to 18% between early and later pregnancy. Although the increase does not reflect a significant change in proportions, increases in anxiety over the course of pregnancy is similar to the evidence observed in international systematic reviews. For example, a systematic review of 102 studies (of which only 4 were from Africa) found meta-analytic rates of 18% and 19% respectively in the first and second trimesters, and increasing up to 24% by the third trimester (39).

Prior to this research three other studies in South Africa had undertaken a careful examination of anxiety in pregnancy and while all were cross-sectional, they had the strength of having used diagnostic measures (35, 41, 42). Unfortunately, one of these

studies did not report diagnostic outcomes or prevelances, but only reported the mean scores for the anxiety scale (41).

The two studies reporting prevalence of antenatal anxiety were both conducted in urban settings – one in Johannesburg, Gauteng and the other in Hanover Park, Western Province. Marsay et al (2013) in Gauteng found a prevalence of 14.5% in the second and third trimester using the SCID, while Van Heyningen in the Western Province found an overall anxiety prevalence of 22% in a high risk, community based sample using the Mini-International Neuropsychiatric Interview (MINI Plus). The latter study noted that some of the cases were attributed to post traumatic stress disorder, while approximately 18% of women presented with more generalised anxiety. While that study included women in all three trimesters, unfortunately rates were not disaggregated or reported by trimester, therefore limiting a more detailed comparison between that research and the results of this research.

Detection of anxiety earlier in pregnancy is important not only for the mother's well-being and care, but because anxiety is known to have effects on fetal development through biological pathways (139). Equally concerning is that anxiety is also associated with cognitive processes such as rumination and the development of distorted perceptions, and in instances where anxiety remains untreated, it can become more difficult to treat later in pregnancy (10).

It is commonly expected that prevalence rates of mental health disorders based on diagnostic measures will be lower than those estimated by screening tools, as is seen in this study (14). As such it is important to note that in this study the use of screening measures may over report risk for clinical disorders such as anxiety, nonetheless the research demonstrates that anxiety is fairly common, and that there is a trend towards increasing anxiety over the course of pregnancy.

6.3.3 Onset and duration of antenatal depression and anxiety

The longitudinal nature of this data allowed for the grouping of women by the timing of onset and duration of their symptoms - those who had early depression or anxiety and recovered, late onset of depression or anxiety, or persistent depression or anxiety. The Venn diagrams in Figure 6.2 illustrate a summary of these groups for both depression and anxiety

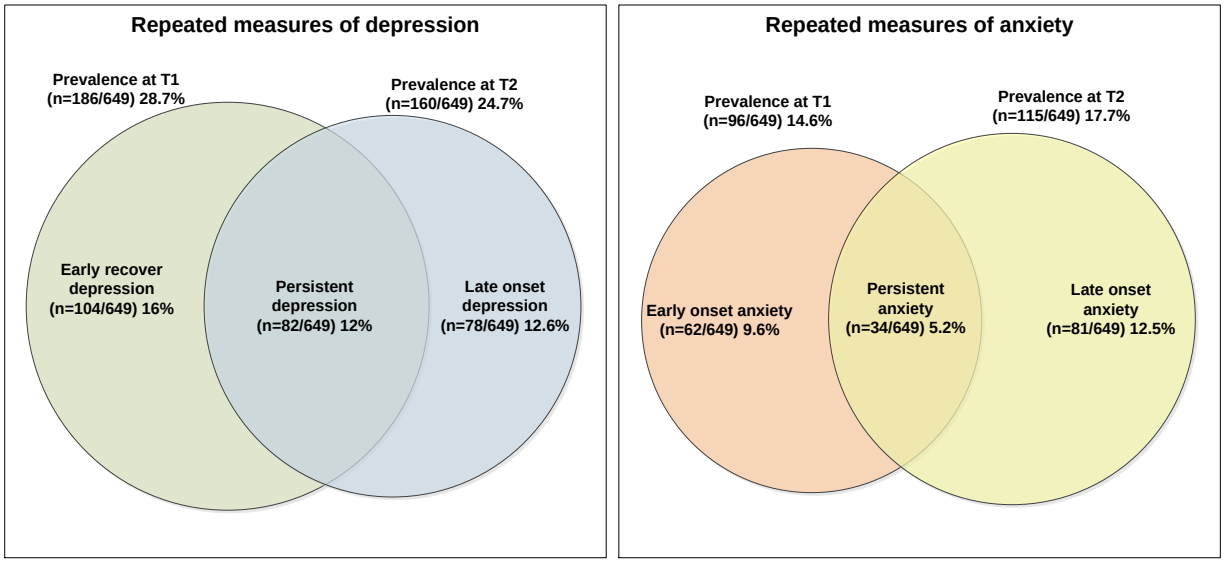

Figure 6.2 Venn diagrams illustrating the groups of women by timing of onset and duration of symptoms

The distribution of cases of depression is fairly even for pregnancy – with about a third of women with depression at some point during pregnancy (82/264; 31%). Anxiety is less persistent, with only a third of early cases persisting into later pregnancy, and most of the women who make up the 17.7% prevalence in later pregnancy are new cases. Some evidence suggests that these persistent syndromes have a poorer response to treatment (140).

6.3.4 The co-morbidity of antenatal depression and anxiety

In this research 7 and 9% of women presented with comorbid depression and anxiety in early and later pregnancy respectively, which is consistent with the few studies which have examined comorbidity in pregnancy (16, 141). Of the 68 women who had comorbid symptoms in early pregnancy, 33% completely recovered and reported no mental health problems later in pregnancy. That a third of women recovered (without a targeted intervention) would suggest that even though they did have features of both disorders, and potentially reported a wider range of symptoms, these cases might not have been as severe or as syndromic as one would expect from the current comorbidity literature (140, 142). The overall decrease in levels of comorbidity between early and later pregnancy is similar to evidence from a meta-analysis of comorbidity in pregnancy (141).

Of the women with comorbid depression and anxiety in later pregnancy, a third had depression in early pregnancy. This suggests that comorbidity may operate in a specific and different way to either depression or anxiety, as was highlighted by the Lancet Perinatal

Mental Health series (2), which found that comorbidity was most often preceded or followed by depression specifically, more so than by anxiety. This is similar to the current understanding of depression with anxious features in the general population (10).

The bi-factor model shows that women whose symptoms were representative of a general depression and anxiety factor were more likely to have thoughts of self-harm later in pregnancy, and implies some level of severity associated with shared depressive and anxious symptoms, although this needs to be balanced against the high rate of recovery described above for co-morbid women. There is support in the literature for the finding that the presence and persistence of comorbid symptoms in pregnancy would likely identify women most at risk for self-harming behaviours, incluing some supporting research on this from LMICs (143). Unfortunately, the lack of literature on comorbidities limits our understanding of the development and resolution of comorbid these symptoms and how best to identify and respond women experiencing them.

6.4 The prevention and mitigation of antenatal depression and anxiety

In this section, the modifiable factors associated with both antenatal depression and anxiety are described and interrogated to establish their potential as intervention or prevention targets in South Africa. The next section will consider entry points within the current healthcare system and those beyond the primary health care setting through which interventions and supports to address perinatal mental health might be implemented.

6.4.1 Partner support in pregnancy in South Africa

When considering the results across the three empirical chapters, it becomes clear that the partner relationship is central to depression in this context. At both timepoints, the variable reflecting the woman's negative perception of her partner – her endorsement of the statement, "my partner makes my life harder," is the variable which is most strongly associated with cases of depression (see Figure 6.3 below). That this item was asked and interrogated alongside measures of more objective negative partner behaviours such as items on partner conflict and partner violence, suggests that this variable captures the emotional qualities of the partner relationship, and pregnancy related support.

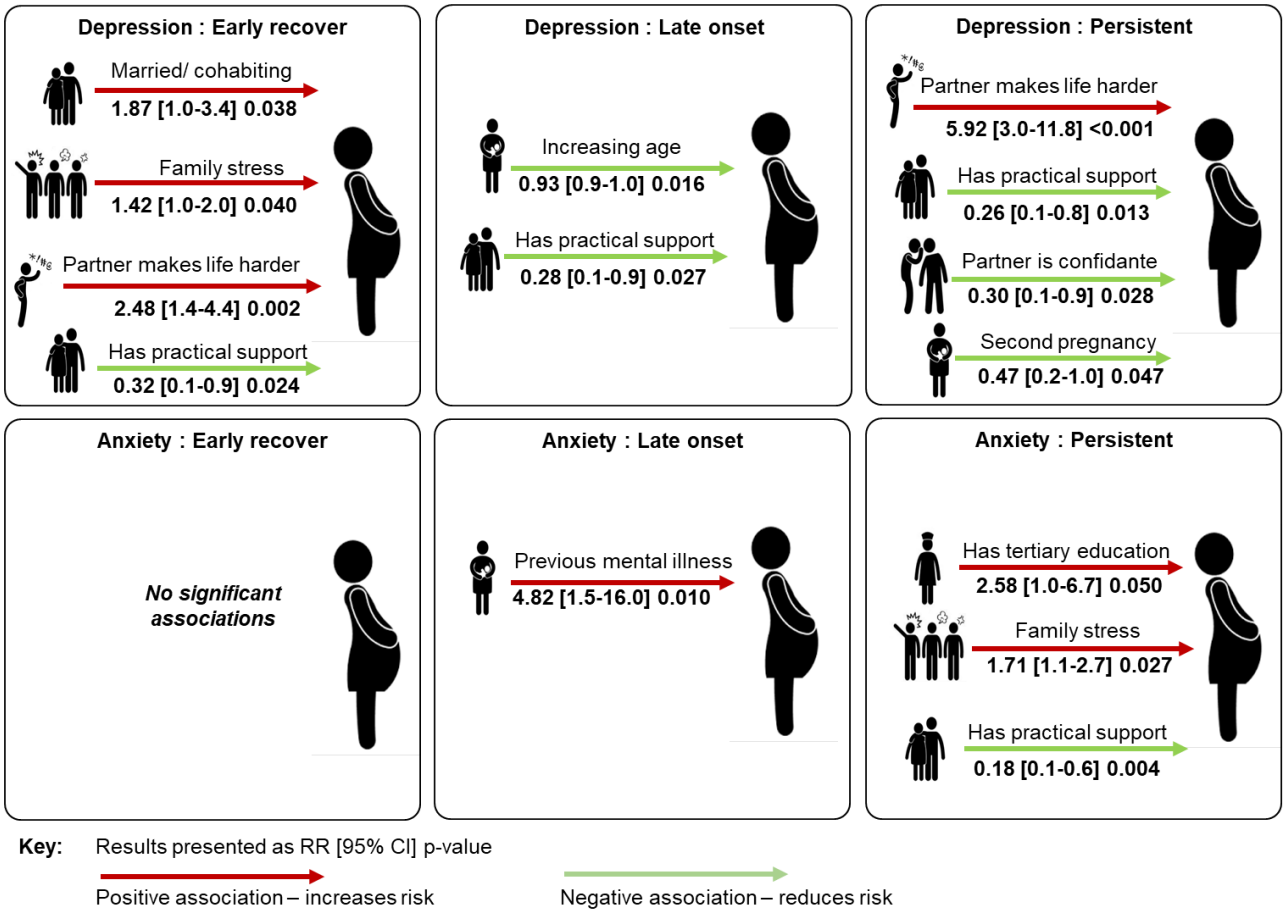

Figure 6.3 Diagram of results of multinomial regression models showing the risk and protective factors associated with depression and anxiety across pregnancy

In the literature, being single or unmarried is a factor which is often associated with antenatal depression and anxiety, while being married is sometimes used as a proxy variable for having an involved partner (122). In this study being single was not associated with either depression or anxiety, however it was associated with reporting 'my partner makes my life harder' with single women more likely to endorse this statement (OR 1.6 95% CI [1.2-2.1] p=0.001). The variable 'my partner makes my life harder' is distinctive from most other studies in that it is not just a life event, nor an indication of the partner's presence or absence, but is rather the pregnant woman's reflection on the effect of her partner's behaviour on her life.

This perception of a difficult partner tripled the odds of being depressed in early pregnancy and doubled the odds in later pregnancy. It also put women at the highest risk for having persistent depression. It is important to consider that the existing literature suggests that antenatal depression may skew perceptions of others, including partners, towards a more

negative outlook (10), for example another study in South Africa found that antenatal depression was associated with the perception that one would be more discriminated against by others (27). In the absence of more detailed data on partner behaviour, and without interrogating the partner relationship more directly, the finding in this study about partners making life difficult should be interpreted cautiously. Ensuring that interpretation is not negatively skewed is important because in this research many items which did enquire more directly about partner positive support (such as whether the woman felt she was able to confide in her partner) substantially lowered risks. The items reporting on practical support which did not specify the source of support but which are also protective, could also plausibly be attributed, if only in part, to the partner. Essentially, without vilifying partners, a clear finding in this research is that unsupportive partners have a particularly detrimental effect on maternal mental health in pregnancy, while the presence and actions of helpful partners are undeniably protective.

6.4.2 Partner involvement in antenatal care and pregnancy

Male partner involvement in antenatal care is associated with improved maternal health outcomes (144), including mental health, with studies from LMICs finding that for women whose partners attended antenatal visits the likelihood of having antenatal depression was reduced by 90% (145, 146), and postnatal depression by 70% (122). There is also evidence from the PMTCT literature in Africa that male partner involvement in antenatal care is beneficial for HIV-positive mothers and their children (147-149). The term ‘male involvement’ is a heterogeneous one, however, it has been suggested that there are three broad categories to consider: 1. Active participation in antenatal services, including support and presence during delivery; 2. Financial support for pregnancy and childbirth expenses; and 3. Making decisions about maternal health together with the partner (122).

While increasing male partner involvement in antenatal care is considered an important aspect in improving maternal health in the literature, it is unfortunately not a focus or priority in many healthcare settings, especially in LMICs (150). There have been few good examples in the South African health care context to model this kind of inclusive approach (121). Some of what makes these efforts difficult, as seen in the HIV and PMTCT literature, is a limited understanding of how to engage male partners, as barriers can be vastly different across different contexts (151). Additionally, in low resource contexts, maternity spaces (both antenatal and delivery spaces) are often shared by groups of unrelated and unfamiliar women, creating difficulties in retaining privacy for individual women while inviting

male partners to participate in activities with their partner in a group setting. Male partners have also reported barriers within healthcare structures including the behaviour of healthcare workers towards them, the timing and duration of visits, and a lack of space for them to accompany their partners to antenatal visits (150, 152).

In South Africa, given pervasive cultural beliefs around child-bearing, these barriers often start at the family level – for example, men are denied access to their pregnant partners if pregnancies occur out of wedlock, and it becomes difficult to be involved in her support and care. in particular in cases of more vulnerable pregnancies such as those that are high risk or unplanned or in situations where the pregnancy has elicited feelings of shame, guilt or anger for women, their partners and families. This limits a partners ability to share in decision making and to provide both emotional and practical support (153).

6.4.3 Social barriers to partner involvement and partner vulnerabilities

As seen in the results of this study, practical support is one of the key factors reducing risk particularly for depression, but also anxiety. A focus on increasing male involvement should not undermine the important role played by families in supporting couples during pregnancies and childbearing. As introduced previously, societal norms in South Africa and many other African settings mean that families often play a central role in the care and provision of emotional and practical support to pregnant women and mothers, often in the absence of partners. This is due in part to traditions such as ‘Lobola,’ which is a bride price paid by men to their partner’s family before marriage between the pair being permitted (154). For many couples, pregnancies occur before the Lobola fee is paid, resulting in family conflict, and in the male partner being distanced from his partner and children. Essentially while the male partner is the father of the child, he is often not considered part of the child’s family.

While there has been particular advocacy for male involvement in perinatal care, in most African cultures the pregnancy and delivery are regarded as a woman’s domain and responsibility. Unfortunately, as highlighted in the 2018 State of South African Fathers report, the negative perceptions of African men (that they are absent, unfeeling, uninvolved or even violent) further alienate them from their partners and children(121).

In addition to male partners being excluded from providing practical family engagement, there is a bias in the literature (outlined in the literature review) towards viewing the partner as largely a negative force in pregnancy in African contexts, however increasing evidence is

showing that they too are vulnerable in the perinatal period. Perinatal depression in men has been shown to be prevalent and highly correlated with partner mental health. Efforts to include male partners in maternal mental health care therefore have the potential to provide double the benefit. In this research the longitudinal nature of the data allowed for an examination of the relationship between depression, anxiety and partner and family stress. The research demonstrates for the first time in an African setting that depression in early pregnancy can lead to increased difficulties in partner relationships. Without concurrent measures of partner depression it is important to consider – given international evidence – that some of these partner difficulties might reflect partner vulnerabilities in response to, or associated with, his partner's depression. Antenatal depression has been shown to be associated with paternal depression in the antenatal and postnatal period (155), and parental depression has in turn been associated with negative child outcomes (120). Successful interventions such as couples counselling and testing for HIV in the perinatal period could be used as an example or possible integration point for mental health screening, promotion, and education in antenatal care services. An example of a novel approach to engaging men in antenatal care services is the Healthy Pregnancy, Healthy Baby study (156) based at CHBAH. The study uses a pregnancy ultrasound visit to share additional information related to fetal and infant development, and the importance of parental wellbeing. While their primary outcome is to assess whether the intervention improves child development, one of their strategies is male partner involvement, which was encouraged by inviting men to attend all study visits, including the fetal ultrasound.

6.4.4 Family involvement in antenatal care

Family stress is associated with both depression and anxiety, and the results of the cross-lagged models show that early family stress results in later anxiety. Partner and family stressors are a key intervention target, not only because negative and stressful relationships elevate risk, but because this research demonstrates that for many women a positive and supportive partner and family relationships can mitigate risk for depression and anxiety, despite living in stressful situations or experiencing stressful and negative life events during pregnancy. Psychological treatments are most often based at healthcare facilities or engage the pregnant woman only; while community-based and home-visiting interventions, which do involve the woman's social support network, tend to engage either the family or the partner, but not both. This dichotomy in the design and implementation of interventions marginalises potential sources of support instead of creating a broader circle of care around

the pregnant woman (and later her child) because partners can compensate for poor family support and vice versa.

6.5 The identification and treatment of antenatal depression and anxiety

In LMIC or low-income areas, the antenatal period can be the only interaction a woman has with the healthcare system for her own health and therefore antenatal visits provide an important opportunity for mental health screening and intervention. Given the scarcity of human resources in our overburdened public health settings, it should be a priority to simplify screening approaches in order to encourage clinicians to engage in identifying at-risk women. At the same time, efforts in improving early identification of mental health risk in pregnancy should be matched with strengthening of current treatment and referral options. This section concludes with a summary of recommendations for interventions to strengthen mental health care and support for antenatal depression and anxiety symptoms within the current South African National Department of Health.

6.5.1 Screening and identification of women in need of care

Currently in South Africa, the Basic Antenatal Care (BANC) strategy is used within Department of Health facilities as the gold standard for antenatal care(157). The BANC Handbook, which is used by medical and nursing students during their studies, as well as by clinicians in routine practice, has been included in the National Department of Health's Guidelines for Maternal Care (1). While the BANC strategy provides checklists for routine antenatal visits and outlines considerations for triaging of care within department of health structures, it fails to include mental health screening or intervention in the perinatal period. It should be noted however that there is increasing advocacy for the inclusion of mental health assessments as part of routine antenatal care – as seen in the South African literature.

Several studies have explored short and ultra-short measures for perinatal depression in South Africa and internationally, and most have shown good sensitivity and specificity when compared to diagnostic measures of depression and anxiety (78, 135, 158). Outside of the perinatal period, a brief tool has been developed and validated for screening of common mental disorders (alcohol use, depression, anxiety) (135). This tool has been used within the primary health care settings and shown high specificity, therefore keeping the number of false positives low and protecting valuable screening and intervention time and resources.

This tool, which is being widely implemented within the South African Department of Health should be tested and validated in perinatal settings.

A unique feature of this research is that it includes items from both depression and anxiety scales and was therefore able to explore the contribution of items from both scales in identifying a general mental health factor in the bifactor model. It allowed me to identify items which would be efficient in identifying women with both depressive and anxious features – which could indicate comorbidity, or a higher risk for TSH. Once identified, women need to be triaged into an appropriate level of care, an area of which has been under-researched in perinatal populations South Africa to date. Findings like this and the recommendations associated with it could be included in medical training curricula as a means to familiarise all medical officers to the simplicity with which mental health concerns can be identified.

6.5.2 Approaches to triaging care by level of risk in South Africa

A clear approach for stratification of women by level of psychological risk could be helpful if applied in public health settings in South Africa. Using data from this study it has been possible to estimate the number of women needing higher levels of care versus those who may be better suited to lower intensity support. In order to examine this the prevalence percentages were averaged across the two timepoints in the study, as differences were non-significant and therefore would be applicable at most points in pregnancy given the stability of disorders demonstrated in this research. Figure 6.4 below describes groups of women according to psychological risk.

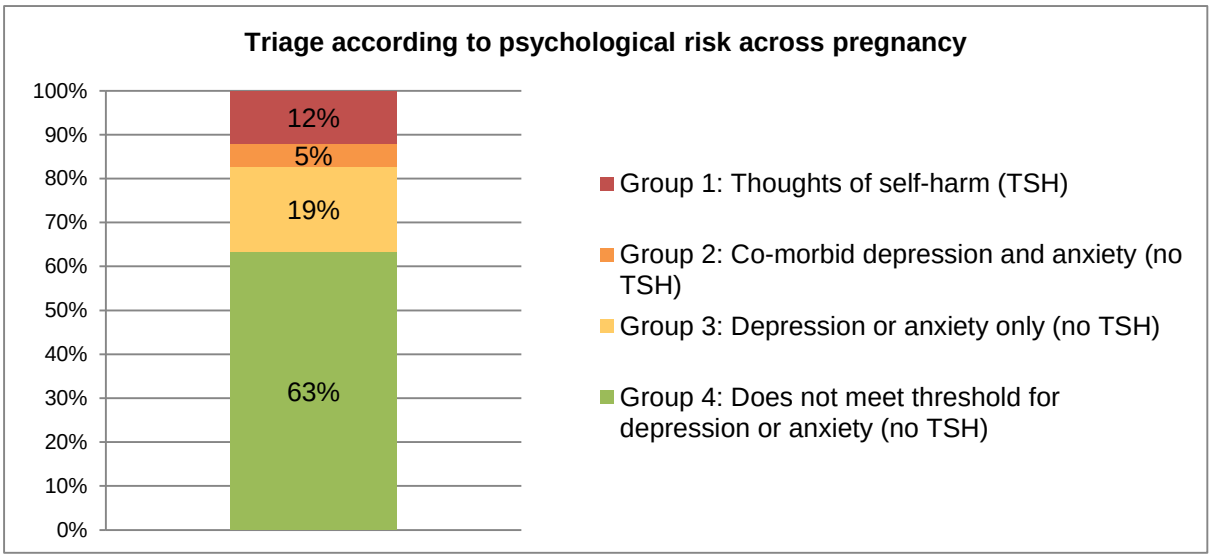

Figure 6.4 Bar chart displaying numbers and percentage of women per psychological risk group (n=649)

Group 1: High risk - high intensity intervention

Women in this group are those at immediate risk needing referral to a professional (medical officer, psychologist, nurse) or para-professional (crisis trained counsellor) before leaving the healthcare facility. In practice, this screening should include a more detailed suicide screening (potentially using some of the tools already identified in the literature) to assess whether TSH are current or have escalated to suicidal intentions or behaviours. Given the limited number of mental health specialists in the country (particularly psychologists and psychiatrists) (159), services might be stretched and could lead to lower-quality care. Strategies shown to improve the quality of care delivered in emergency departments managing perinatal psychiatric emergencies include the creation of multidisciplinary teams (including medically trained professional and non-professional staff) who are provided with specialist training and who work to efficiently identify and manage risk within the health care setting (160).

Following emergency care, referral into step-down care within the community and family is also critical to preventing relapse. South Africa needs to strengthen the process of task-shifting of perinatal mental health interventions at a community level given to receive these referrals, and manage ongoing care of these women as well as those with moderate risk.

The Perinatal Mental Health Project (PMHP) at Mowbray Maternity Hospital is an example of this type of stepped care. In this project, women were screened for depression (a score of ≥13 EPDS) and other risk factors during routine antenatal visits. If they were found to be at high risk, they are immediately referred to a psychiatrist. Women with moderate symptoms are referred for counselling at the hospital with a lay counsellor, which they attend at subsequent antenatal appointments. If a woman is identified as needing specialist intervention at any stage during counselling, she is referred to an onsite psychiatrist who is available at the antenatal clinic once every two weeks. This model used by PMHP illustrates that an appropriately trained multi-disciplinary mental health team can screen for and treat depression, while reducing burden on scarce specialised services. A key component of a successful stepped approach is the quality of referrals between levels of care, which has been identified as weak within public mental health services in South Africa but has been

successfully implemented in others - such as the Integrated Management of Acute Malnutrition Programme.

Outside of the perinatal period, The PRogramme for Improving Mental health carE (PRIME) has examples from across various LMIC on how mental health services can be successfully integrated into existing programmes (such as TB and HIV) (48). These models could be used and applied to perinatal contexts as they have been very successful in improving adherence to health care, and in integrating mental health care into routine health care. Since many of these models have been tested directly in South Africa health care facilities, using Department of Health systems, they are likely feasible and able to be replicated within antenatal services.

Group 2 and 3: Moderate risk – medium intensity

While asking about thoughts of self-harm is helpful in identifying the need for an emergency response if it was the only mental health question asked of antenatal attendees, there would be approximately 5% of women with symptoms severe enough to meet the criteria for co-morbid depression and anxiety who would be missed. In the same way, 19% of women who would meet the criteria for either one of the disorders would also not be identified. While these women might not be at immediate risk for self-harm or suicide, their symptoms put them at high risk for worsening mental health, and poor health outcomes linked to non-compliance with antenatal appointments, risk of substances use (alcohol and tobacco) during pregnancy (2), which compromise not only their own health but also that of their fetus (4).

Both depression and anxiety can be treated in pregnancy and can be delivered by individuals with varying levels of qualifications - from professionals through to para-professionals. Therapies such as Interpersonal Psychotherapy (IPT), Cognitive Behavioural Therapy (CBT) and Behavioural Activation (BA) have been shown to have good treatment effects (161). Both BA and to a lesser extent CBT, have been demonstrated to be suitable for use in low resourced settings, delivered through lay professionals in a task shifting approach (159, 162). In South Africa there has been one recent randomised control trial (RCT) testing a psychological treatment delivered through task-sharing for antenatal depression, however it did not report significant effects on maternal mood (163). There is also currently another RCT trial underway in KwaZulu-Natal testing behavioural activation delivered

through home-visiting by trained lay therapists as a treatment for antenatal depression (164).

Group 3: Prevention and health promotion

The 63% of women who would not meet the criteria for either depression or anxiety during their visit, and who do not have thoughts of self-harm, represent those women or are either coping well, or those at-risk for later mental health problems - both groups would benefit from a mental health prevention and promotion programme.

As part of their maternal and child health services, the South African National Department of Health (NDoH) has developed and uses an initiative called MomConnect. It is a cellphone-based technology, which facilitates the electronic registration of pregnancies into the public health system, and allows for targeted health promotion messages to be sent to pregnant women. Pregnant women receive free weekly SMS messages throughout their pregnancy and for the first year of the child's life. There is also an interactive mechanism by which women can feedback on the service they have received during antenatal care visits. While the messages for women who have suffered a miscarriage contain mood related content, there are currently no emotional wellbeing or mental health related messages (such as mood monitoring) sent to pregnant women. As a preventative strategy, it is a missed opportunity that women are not receiving messages about common risk factors, or signs and symptoms of mental health problems, given the rates found in this study. As an early screening aid, MomConnect could be utilised to encourage women with symptoms to seek help, or to mention these symptoms to their healthcare provider at their next antenatal visit. MomConnect is already positioned as an ideal platform for the integration of mental health messaging given that 95% of SA's health facilities are using MomConnect and 2 million women have registered for the service (as of August 2020) (165), and that the platform was established with the aim of improving the health of pregnant women and their infants.

6.5.3 Recommendations for interventions in South Africa

As mentioned, task-shifting of mental health care services to trained lay health care workers (particularly psychosocial interventions) has been strongly advocated for in South Africa given the deficit of mental health specialists (psychologists and psychiatrists) (159).

A 2014 review found that psychosocial interventions could be effectively task-shifted to non-specialist health workers in public mental health services in South Africa (166). Of the 5

interventions delivered to pregnant women, only one used a psychological treatment to target depression specifically (problem solving therapy, behavioural activation and relaxation techniques) however the results of this study were recently published, and found no effect on depressive symptoms (163). This evidence, as well as the interventions discussed above have shown that these interventions are possible, and that community health workers are perfectly positioned to take on task-shifted mental health care services in a stepped approach, given the correct training and supervision.

Based on the results of this study, the inclusion of male partners in antenatal care, as well as strengthening of partner and family literacy around the impact of stress on the mental health of women, are also a key intervention targets.

6.6 Considering the COVID-19 pandemic

While the data collection and analysis for this study was completed prior to the outbreak of the global COVID-19 pandemic in early 2020, it would be remiss not to acknowledge the effect that it has had on perinatal mental health in this thesis. Studies which have been conducted during the COVID-19 pandemic have shown elevated symptoms of antenatal depression and anxiety when compared to similar cohorts conducted before the pandemic. A rapid review of antenatal depression and anxiety during the COVID-19 pandemic (December 2019-February 2021) found 37 studies of depression (n=47677), and 34 studies of anxiety (n=42773) (167). Unfortunately none of the 22 countries represented in this dataset were from the African continent. The pooled prevalence of depression was 25.6%, while pooled prevalence for anxiety was 30.5%, and the authors noted that prevalence of anxiety was higher later in the pandemic. These rates are higher than historical prevelances for both disorders, and it is interesting to note that rates of anxiety are higher than depression – which it not the norm in the literature (15).

Higher rates of anxiety during the pandemic, even in the general population, have been attributed to concern over contracting COVID-19, and therefore the health of both the pregnant mother and her baby. In many countries, national restrictions have meant that women have had to attend antenatal visits (including ultrasounds) alone, and during severe lockdown periods, have also had to endure labour and delivery without their male partners or a family member in attendance (168). Social isolation, especially in areas which have experienced prolonged lockdown restrictions, has not only affected perceived support, but

also the ability of support networks to provide necessary support to vulnerable pregnant women.

Following the global COVID-19 pandemic, many antenatal mental health interventions, especially hospital-based ones, will need to be revisited and reconsidered. The numerous restrictions on movement and other regulations have necessitated that clinicians and researchers move to remote delivery of their services wherever possible. This most often requires that the healthcare system delivering the intervention has capacity, and that the clients have necessary communication devices (phones, tablets, laptops) and data. While well-resourced countries have the ability to move home based mental health care to telephonic or digital platforms, this is not likely in LMICs, including in Africa. In South Africa there is the South African Depression and Anxiety Group (SADAG) helpline which is a form of remote counselling for depression and/or other emotional problems, but this kind of intervention would be difficult (if not impossible) to deliver within the current public healthcare system in South Africa and other similar economies.

Chapter 7 : Conclusion

7.1 Introduction

In this final chapter of the thesis, the strengths and limitations of this work will be discussed, and potential future research questions are posed. Lastly, a summary of the findings and contribution are stated in the conclusion.

7.2 Strengths of the research

Prior to undertaking this study, the literature showed that antenatal depression and anxiety were common globally. Evidence on antenatal depression in LMICs, and in Africa in particular is relatively limited compared to HICs (2, 12, 15), and there is very little evidence on antenatal anxiety. I have been unable to find another African study of antenatal depression and anxiety specifically during the first trimester of pregnancy – although some studies did include women who were in the first trimester in the overall sample (12, 19). Also, no studies had looked at a change in antenatal depression and anxiety cases concurrently across pregnancy, and interrogated the factors associated with timing and onset in a pregnant population. Having longitudinal data on a single sample, starting in the first trimester, allowed me to compare prevalence across pregnancy as well as create groups according to timing of onset and therefore interrogate the patterns of emergence and recovery across pregnancy.

In recent years, longitudinal cohorts such as the Avon Longitudinal Study of Parents and Children (ALSPAC) have begun to use structural equation modelling to interrogate mechanistic and causal pathways in disorders like depression and anxiety. This PhD is methodologically innovative in that it is the first application of cross-lagged panel analysis and bifactor model to examine depression and anxiety in pregnancy in Africa to date.

Having continuous data on depression, anxiety and stress at two timepoints in pregnancy allowed me to use crosslagged modelling to investigate the direction of effect between these constructs. Prior to this study, the literature in South Africa was only able to determine associations between these three constructs in pregnancy as at least two timepoints are needed for all constructs in order to determine directionality. The bifactor models tested whether the covariance among the item responses on the depression and anxiety scales (EPDS and STAI) were better accounted for by a single global construct, or by their two specific factors (depression and anxiety). This type of analysis would not have been possible had I not measured both depression and anxiety concurrently, and I have been

unable to find another study in Africa which has used the same technique to investigate the latent general factor.

7.3 Limitations of the research

There are a number of different screening and diagnostic tools used for determining cases of depression and anxiety across both research and clinical settings. While the structured clinical interview is considered the 'gold standard' for diagnosing both depression and anxiety, it requires a high level of skill and a significant amount of time to complete and analyse – making its use difficult in research settings. The use of screening tools instead of diagnostic measures is common in both research and clinical settings, although the use of screening tools has the limitation of being less definitive in identifying clinical symptoms and can therefore over or underestimate risk, in particular if they have not been well validated prior to use or when non-standardised approaches to scoring are used.

A recent meta-research review comparing depression prevalence estimates in meta-analyses based on screening tools and rating scales versus diagnostic interviews showed that the EPDS might overestimate prevalence of depression by between 3.3% (at a true prevalence of 5%) and 1.6% (at a true prevalence of 15%) (169). This difference in prevalence therefore decreases as the true prevalence increases – meaning that at rates found in this research of between 24.7% to 28.7% difference would be closer to 1%. While I have been unable to find similar estimates for differences in anxiety prevalence between screening tools and clinical interviews, it should be noted that anxiety estimates across the literature are more diverse.

The EPDS and STAI-short form were chosen for this study as they are widely used, and the EPDS particularly has been well validated in LMICs and in South Africa. During data analysis, I used the internationally accepted and locally validated cut-offs for both the EPDS and the STAI (79, 82). The EPDS has been validated against the structured clinical interview in South Africa and has been shown to be the most reliable screening tool for antenatal and postnatal depression in South African populations (104). The reliability statistics for both measures were acceptable at each timepoint, and crosslagged models showed stability in the constructs.

The lack of paternal mental health data in this sample presents a limitation to our understanding of the potential bidirectional or causal pathways between maternal and

paternal mental health. This is especially relevant given that maternal and paternal mental health in the perinatal period are highly correlated (155), and the findings in the study around the strength of association between the partner relationship and maternal mental health.

Although TSH was measured using a realible and validated tool, a limitation of this research is that data was not collection on suicidality, and therefore I cannot report on suicidal ideation, suicidal behaviour and plans. Additionally, no questions were asked about previous history of TSH, which have been shown in the literature to predict later suicidality (170).

7.4 Future research

Studies, mostly from HICs have shown that depression and anxiety during pregnancy can impact on offspring even into adulthood. Future research in Soweto could aim to determine the impact of antenatal depression and/or anxiety on child developmental outcomes. Having evidence of this effect would add weight to funding and intervention initiatives focusing on the pregnancy period because it highlights the role of the mother or caregiver in providing the best environment for her child (considering the aims of global programmes such as the Nurturing Care Framework for Early Childhood Development, which is “helping children survive and thrive to transform health and human potential” (171).

Many South African studies have used the EPDS to measure depression, and therefore would have the same data on TSH in their data sets as I have reported on as the variable was created using EPDS item 10. Some other depression scales also ask about TSH. Future research could attempt to pool EPDS data from this and other South African studies in order to examine rates of TSH across different contexts.

Knowing that fathers (or male partners) are vulnerable to perinatal depression and anxiety (120) , further research should include an assessment of their mental health with that of their partner’s mental health. Further to this, qualitative investigations into both partner’s accounts of their relationship, and what variables such as ‘my partner makes my life harder’ might be describing in terms of relationship satisfaction or conflict. This would lead to an understanding of whether interpersonal relationships would be an acceptable and feasible intervention point for perinatal mental health promotion and prevention in Soweto and other parts of South Africa. These kind of investigations could also include explorations of

whether family members such as mothers or mother in law were also seen to make life harder in response to unplanned pregnancies.

7.5 Conclusion

South African women enter pregnancy at high risk for mental health disorders, due to the high stress contexts they are living in, however a large proportion of these risks can be attenuated if women are adequately and appropriately supported by partners, families or close social networks. It should be possible to triage women according to level of psychological risk within primary health care settings using short, simple screening tools.

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APPENDICES

Appendix A: S1000 data collection tools relevant to the PhD

FV: SSS

University of the Witwatersrand, Johannesburg
Developmental Pathways for Health Research Unit
Department of Paediatrics and Child Health

Soweto Fetal Growth Study
SOCIAL SUPPORT AND STRESS QUESTIONNAIRE (SSS) 2013

BTT ID: _____

(Her or her ♂ partner's BTT ID)

Partner ID: _____

(♀partner of a ♂ BTT participant)

3G ID: _____

Or

INTERBIO ID: _____

Or

SFG ID: _____

Interviewer's name: _____

Interview date: _____

Social Support questions from the Antenatal (9)

In order for us to be able to understand your particular circumstances better, we would like to know how much help and support you feel you get from your family and friends.

1. If you had a really big problem and needed help with money, the children, accommodation and so on, are there people who could help you?

Nobody = 1	Maybe / unsure = 2	A number of people = 3

2. Can you talk to your parents, other family members or friends about any problems you may have?

Nobody = 1	Maybe / unsure = 2	A number of people = 3

3. Can you talk to your husband or partner about any problems you might have?

Never = 1	Sometimes = 2	Always = 3

4. Some people think the sisters at the clinic are always helpful, others think only sometimes and some say they are seldom helpful. How do you feel?

Always helpful = 1	Sometimes helpful = 2	Seldom helpful = 3

5. Do you feel that the father of your child or your partner makes things harder for you because of the way he acts?

Never = 1	Sometimes = 2	Always = 3

6. Do you belong to a church group or any other organisation?

Yes = 1	No = 2

7. How often do you go to meetings?

Once a week = 1	Once a month = 2	Irregularly = 3

8. Do you have a friend who is also going to have a baby or has just had a baby?

Yes = 1	No = 2

9. If **YES**, how often do you see her?

Once a week = 1	Once a month = 2	Irregularly = 3

Spielberger State Anxiety Scale (6)

A number of statements which people have used to describe themselves are given below. I will read you each statement and I would like for you to indicate how you feel *right now,* that

is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

(Use same scoring system as above: **1** = disagree **2** = neutral **3** = agree **4** = strongly agree)

1. I feel calm…… 1 2 3 4
2. I am tense…… 1 2 3 4
3. I feel upset…… 1 2 3 4
4. I am relaxed…… 1 2 3 4
5. I feel content…… 1 2 3 4
6. I am worried…… 1 2 3 4

Antenatal Stress Questionnaire (16)

Sometimes one's life and that of one's close family goes through periods of being very stressful. I'd like to ask you some questions about any stresses you might have experienced in the last few months.

1. During the last 6 months have you or a member of your close family been in real danger of being killed, in one of the following ways?

1 = By criminals
2 = By police, army or other 'officials'
3 = During political activities
4 = This has not happened at all

2. During the last 6 months did you witness a violent crime (e.g. murder, robbery, assault, rape)?

Yes = 1	No = 2

3. During the last 6 months have you found that you are in so much debt that you don't know how you will repay the money?

Yes = 1	No = 2

4. During the last 6 months have you or your close family ever had too little money for basics, such as food, rent, and clothes?

Yes = 1	No = 2

5. Have you or one of your close family not been able to find a job for more than 6 months?

Yes = 1	No = 2

6. During the last 6 months have you or anyone in your close family been seriously ill?

Yes = 1	No = 2

7. During the last 6 months did any member of your close family die?

Yes = 1	No = 2

8. Is there anyone in your close family with a serious disability (e.g. epilepsy, mental retardation, deafness, blindness, mental illness)?

Yes = 1	No = 2

9. Is there anyone in your close family who has a problem with drugs or alcohol?

Yes = 1	No = 2

10. During the last 6 months have you had a break-up with your husband or partner?

Yes = 1	No = 2

11. During the last 6 months has your husband or partner hit or beaten you?

Yes = 1	No = 2

12. During the last 6 months have you had any serious fight or alienation from members of your family or your close neighbours?

Yes = 1	No = 2

13. During the last 6 months have you or any member of your close family been arrested, had to go to court or consulted a lawyer on a non-routine matter?

Yes = 1	No = 2

14. During the last 6 months have you given help (money, accommodation etc.) to close family or friends in need?

Yes = 1	No = 2

15. During the last 6 months have you been separated unwillingly from any of your children (excluding holidays)?

Yes = 1	No = 2

16. During the last 6 months have you experienced any problems with your other children (such as schools closing, failure at school, problem behaviour, drugs, etc.)?

Yes = 1	No = 2	No other child = 3

If YES, specify problem _____

Edinburgh Depression Scale (EPDS) (10)

Please mark the answer which comes closest to how you have felt in the past 7 days, not just how you feel today.

1. I have been able to laugh and see the funny side of things.	___ As much as I always could
	___ Not quite so much now
	___ Definitely not so much now
	___ Not at all
2. I have looked forward with enjoyment to things.	___ As much as I ever did
	___ Rather less than I used to
	___ Definitely less than I used to
	___ Hardly at all
3. I have blamed myself unnecessarily when things went wrong.	___ Yes, most of the time
	___ Yes, some of the time
	___ Not very often
	___ No, never
4. **I have been anxious or worried for no good reason.**	___ No, not at all
	___ Hardly ever
	___ Yes, sometimes
	___ Yes, very often
5. **I have felt scared or panicky for not very good reason.**	___ Yes, quite a lot
	___ Yes, sometimes
	___ No, not much
	___ No, not at all
6. Things have been getting on top of me.	___ Yes, most of the time I haven't been able to cope at all
	___ Yes, sometimes I haven't been coping as well as usual
	___ No, most of the time I have coped quite well
	___ No, I have been coping as well as ever
7. I have been so unhappy that I have had difficulty sleeping.	___ Yes, most of the time
	___ Yes, sometimes
	___ Not very often
	___ No, not at all
8. **I have felt sad or miserable.**	___ Yes, most of the time
	___ Yes, quite often
	___ Not very often
	___ No, not at all
9. **I have been so unhappy that I have been crying.**	___ Yes, most of the time
	___ Yes, quite often
	___ Only occasionally
	___ No, never
10. The thought of harming myself has occurred to me.	___ Yes, quite often
	___ Sometimes
	___ Hardly ever
	___ Never

Appendix B: Soweto Fetal Growth Study (SFGS) ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Professor Shane Norris

CLEARANCE CERTIFICATE	**M120524**
PROJECT	Foetal Growth Study: Investigating Maternal Factors Associated with Foetal Growth and Delivery Outcomes
INVESTIGATORS	Professor Shane Norris.
DEPARTMENT	Developmental Pathways Research Unit
DATE CONSIDERED	25/05/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 14/07/2013 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

Appendix C: Masters study (M160670) ethical clearance certificate

R14/49 Ms Stephanie Redinger

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160670

NAME: (Principal Investigator)	Ms Stephanie Redinger
DEPARTMENT:	School of Clinical Medicine Developmental Pathways Health Research Unit
PROJECT TITLE:	Examining the Psychometric Properties of Depression and Anxiety Measures in Early Pregnancy, in a Large Population Based Study of Pregnant Women in Soweto
DATE CONSIDERED:	24/06/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Shane Norris and Dr Tamsen Rochat
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/07/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year.

Principal Investigator Signature

Date 25/06/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D: PhD study (M180949) ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Ms Stephanie Redinger

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180949

NAME: (Principal Investigator)	Ms Stephanie Redinger
DEPARTMENT:	Paediatrics Developmental Pathways for Health Research Unit Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Antenatal depression and anxiety and their association with birth and child outcomes in urban black South Africans
DATE CONSIDERED:	28/09/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Tamsen Rochat and Shane Norris
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/04/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

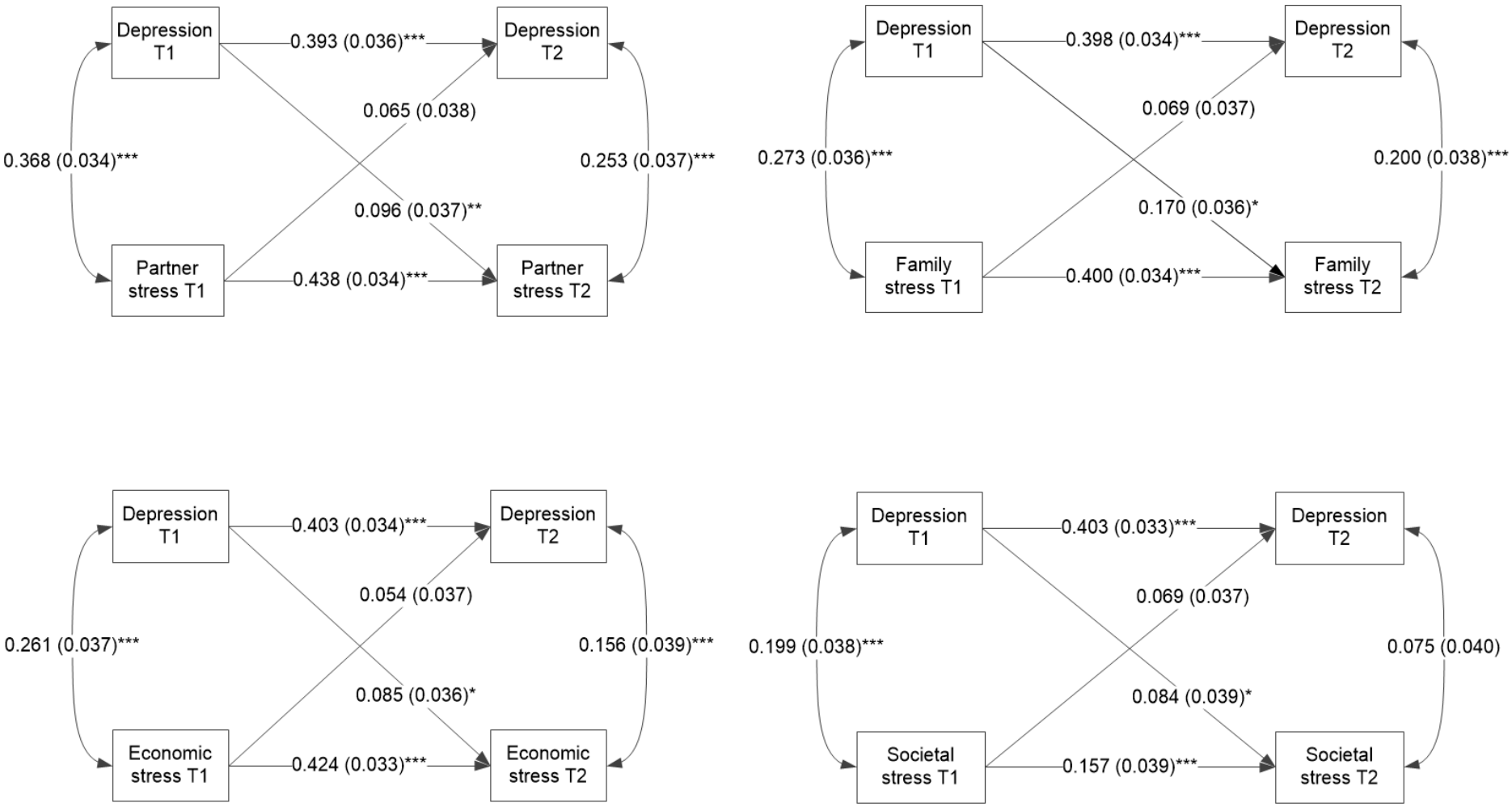
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

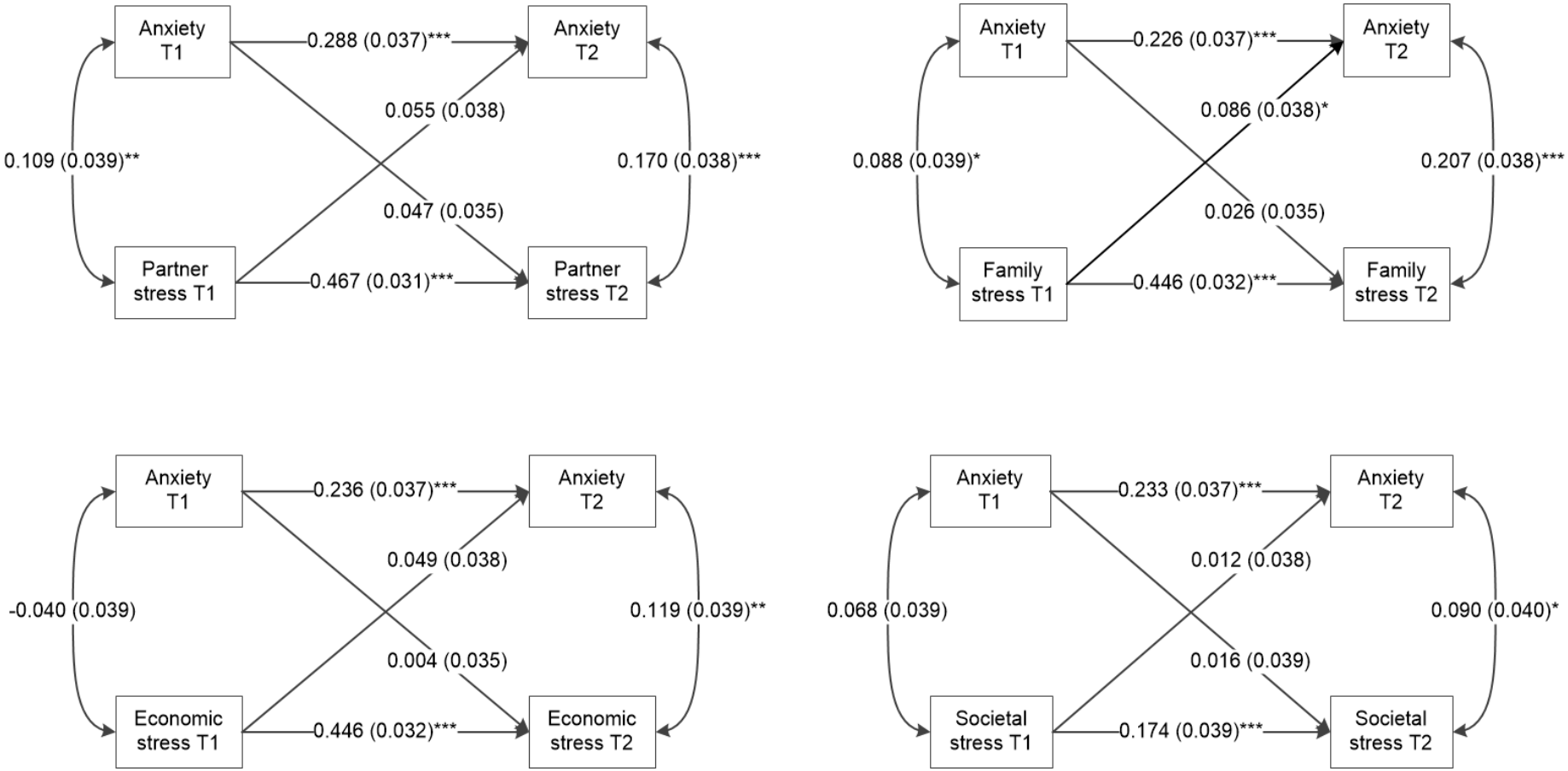
30/04/2019
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix E: Supplementary tables and figures



Supplementary figure S1: Cross-lagged panel model of depression and partner, family, economic and societal stress.
Note: Correlation co-effecients reported as B (SE)
*p<0.050; **p<0.010; ***p<0.001



Supplementary figure S2: Cross-lagged panel models of anxiety and partner, family, economic and societal stress.
Note: Correlation co-effecients reported as B (SE)
*p<0.050; **p<0.010; ***p<0.001

Supplementary table 4.1: Changes in social support and stressors

	T1	**T2**	**p-value**
Social support	%	%	z-test
Has practical support	92 .4	94 .9	0 .066
Has confidante	94 .0	95 .1	0 .393
Partner is confidante	94 .6	94 .1	0 .713
Clinic staff are friendly	91 .9	92 .1	0 .886
Partner makes life harder	38 .5	44 .0	**0 .042**
Regular attendance at community organisation	56 .8	57 .6	0 .784
Reguarly sees friend with baby	35 .1	39 .9	0 .075
Stressors	**Mean**	**Mean**	**ttest**
Marital stress*	0 .20	0 .16	0 .010
Family stress**	0 .65	0 .53	<0 .001
Economic stress**	1 .33	1 .11	<0 .001
Societal stress*	0 .14	0 .11	0 .144

*marital stress and societal stress are continuous variables (0-2)
**family stress and economic stress are continuous variables (0-3)

Supplementary table 4.2 Cross sectional T2 logistic regression (complete case)

	aOR Depression	**aOR Anxiety**
	OR [95% CI] p-value	
Age*	0,99 [1,0 - 1,0] 0,748	1,02 [1,0 - 1,1] 0,526
Education		
Primary/ secondary	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Tertiary/ professional	0,71 [0,4 - 1,2] 0,207	1,50 [0,9 - 2,6] 0,147
Relationship status		
Single	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Married/ cohabiting	1,05 [0,6 - 1,7] 0,855	1,33 [0,8 - 2,3] 0,294
People in household		
≤3	1.00 [1.0-1.0]	1.00 [1.0-1.0]
≥4	0,92 [0,6 - 1,5] 0,723	1,14 [0,7 - 1,9] 0,619
Children < 5 years		
No children < 5 years	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Children <5 years	0,99 [0,6 - 1,6] 0,961	**0,57 [0,3 - 1,0] 0,044**
Asset score*	0,94 [0,8 - 1,1] 0,480	1,02 [0,8 - 1,2] 0,834
Parity		
1st pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]
2nd+ pregnancy	0,76 [0,4 - 1,3] 0,303	0,64 [0,4 - 1,2] 0,136
Reproductive intention		
Unplanned pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Planned pregnancy	0,89 [0,6 - 1,4] 0,619	0,92 [0,6 - 1,5] 0,746
Smoked (last 3 months)		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1,19 [0,6 - 2,5] 0,643	0,59 [0,2 - 1,4] 0,245
Alcohol use		
No alcohol use	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Weekly alcohol use	0,98 [0,5 - 2,0] 0,955	**2,13 [1,1 - 4,3] 0,032**
Mental illness (previous)		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1,12 [0,4 - 3,5] 0,843	**4,37 [1,5 - 12,4] 0,006**
HIV status		
HIV Negative	1.00 [1.0-1.0]	1.00 [1.0-1.0]
HIV positive	1,16 [0,7 - 1,9] 0,534	0,71 [0,4 - 1,2] 0,238
Antenatal stressors**		
Marital stress	1,39 [0,8 - 2,3] 0,208	1,51 [0,9 - 2,6] 0,141
Family stress	**1,57 [1,2 - 2,1] 0,002**	**1,68 [1,2 - 2,3] 0,001**
Economic stress	**1,25 [1,0 - 1,6] 0,047**	1,14 [0,9 - 1,5] 0,296
Societal stress	1,13 [0,6 - 2,1] 0,695	1,48 [0,8 - 2,8] 0,231
Has practical support		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0,65 [0,3 - 1,7] 0,367	0,43 [0,2 - 1,1] 0,090
Has confidante		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1,10 [0,4 - 3,0] 0,848	1,10 [0,4 - 3,2] 0,861
Partner is confidante		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1,59 [0,7 - 3,8] 0,301	2,49 [0,9 - 7,0] 0,083
Clinic staff are friendly		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0,97 [0,4 - 2,1] 0,939	0,63 [0,3 - 1,4] 0,248
Partner makes life harder		
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	**3,46 [2,2 - 5,5] 0,000**	**2,46 [1,5 - 4,1] 0,001**
Community organisation		
Does not attend/ irregularly	1.00 [1.0-1.0]	
Attends regularly	0,86 [0,6 - 1,3] 0,501	0,70 [0,4 - 1,1] 0,129

Has friend with baby		
No or sees irregularly	1.00 [1.0-1.0]	
Yes, sees regularly	**0,60 [0,4 - 0,9] 0,024**	0,79 [0,5 - 1,3] 0,341

Supplementary Table 3 : Factors associated with depression by pattern of onset and recovery across pregnancy

	Early-recover		Late onset		Persistent	
	RR [CI] p	**ARR [CI] p**	**RR [CI] p**	**ARR [CI] p**	**RR [CI] p**	**ARR [CI] p**
Age*	0.97 [0.9-1.0] 0.069	0.95 [0.9-1.0] 0.073	0.97 [0.9-1.0] 0.135	**0.93 [0.9-1.0] 0.016**	0.97 [0.9-1.0] 0.113	0.99 [0.9-1.1] 0.832
Education						
Primary/ secondary	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Tertiary/ professional	0.98 [0.6- 1.6] 0.917	1.10 [0.6-2.1] 0.757	0.73 [0.4-1.3] 0.270	0.86 [0.4-1.7] 0.660	**0.37 [0.2-0.7] 0.003**	0.49 [0.2-1.1] 0.092
Relationship status						
Single	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Married/ cohabiting	1.11 [0.7-1.7] 0.647	**1.87 [1.0-3.4] 0.038**	0.97 [0.6-1.6] 0.902	1.17 [0.6-2.2] 0.619	0.69 [0.4-1.2] 0.160	1.19 [0.6-2.4] 0.626
People in household						
≤3	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
≥4	0.94 [0.6-1.5] 0.785	0.95 [0.5-1.7] 0.878	1.18 [0.7-1.9] 0.514	1.23 [0.7-2.3] 0.509	1.11 [0.7-1.8] 0.678	1.05 [0.5-2.1] 0.894
Children < 5 years						
No children < 5 years	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Children <5 years	1.36 [0.9-2.1] 0.193	1.39 [0.8-2.5] 0.280	1.34 [0.8-2.2] 0.265	1.23 [0.7-2.3] 0.504	1.33 [0.8-2.2] 0.269	1.28 [0.6-2.6] 0.480
Asset score*	0.96 [0.8-1.1] 0.549	0.86 [0.7-1.1] 0.157	0.89 [0.8-1.0] 0.130	0.91 [0.7-1.1] 0.410	0.88 [0.8-1.0] 0.109	0.83 [0.7-1.1] 0.133
Parity						
1st pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
2nd+ pregnancy	0.79 [0.5-1.3] 0.344	0.70 [0.4-1.4] 0.301	0.88 [0.5-1.5] 0.658	1.56 [0.7-3.4] 0.257	**0.56 [0.3 -0.9] 0.027**	**0.47 [0.2-1.0] 0.047**
Reproductive intention						
Unplanned pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	
Planned pregnancy	0.69 [0.4-1.1] 0.096	0.72 [0.4-1.3] 0.253	0.89 [0.5-1.5] 0.646	0.75 [0.4-1.3] 0.334	0.64 [0.4-1.0] 0.077	0.73 [0.4-1.4] 0.351
Smoked (last 3 months)						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1.41 [0.7-3.0] 0.375	0.61 [0.2-1.9] 0.384	1.10 [0.4-2.8] 0.832	0.62 [0.2-2.6] 0.514	**2.73 [1.4-5.5] 0.005**	0.85 [0.3-2.5] 0.774
Alcohol use						
No alcohol use	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Weekly alcohol use	1.15 [0.6-2.2] 0.688	0.95 [0.4-2.3] 0.903	1.02 [0.5-2.2] 0.963	1.40 [0.6-3.4] 0.461	1.02 [0.5-2.2] 0.963	0.79 [0.3-2.3] 0.672

Mental illness (previous)						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1.89 [0.6-6.4] 0.309	1.88 [0.5-7.6] 0.374	1.24 [0.3-6.0] 0.788	1.92 [0.3-10.8] 0.460	1.79 [0.5-6.9] 0.398	2.62 [0.5-12.7] 0.231
HIV status						
HIV Negative	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
HIV positive	1.46 [0.9-2.3] 0.112	1.42 [0.8-2.6] 0.252	1.09 [0.6-1.9] 0.764	1.15 [0.6-2.3] 0.675	1.18 [0.7-2.0] 0.536	1.22 [0.6-2.4] 0.566
Antenatal stressors**						
Marital stress	**2.29 [1.5-3.6] 0.000**	1.26 [0.7-2.3] 0.444	0.76 [0.4-1.6] 0.462	0.53 [0.2-1.3] 0.173	**3.50 [2.2-5.5] 0.000**	1.70 [0.9-3.1] 0.079
Family stress	**1.62 [1.2-2.1] 0.000**	**1.42 [1.0-2.0] 0.040**	0.89 [0.6-1.3] 0.508	0.74 [0.5-1.2] 0.182	**1.97 [1.5-2.6] 0.000**	1.38 [0.9-2.0] 0.100
Economic stress	**1.39 [1.1-1.7] 0.005**	1.20 [0.9-1.6] 0.234	1.24 [1.0-1.6] 0.099	1.16 [0.8-1.6] 0.354	**1.73 [1.3-2.2] 0.000**	1.26 [0.9-1.8] 0.203
Societal stress	1.51 [0.9-2.6] 0.120	1.26 [0.6-2.5] 0.507	1.05 [0.5-2.1] 0.891	0.82 [0.3-2.0] 0.656	**1.95 [1.2-3.3] 0.011**	1.78 [0.9-3.6] 0.109
Has practical support						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	**0.24 [0.1-0.5] 0.001**	**0.32 [0.1-0.9] 0.024**	**0.27 [0.1-0.7] 0.004**	**0.28 [0.1-0.9] 0.027**	**0.17 [0.1-0.4] 0.000**	**0.26 [0.1-0.8] 0.013**
Has confidante						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	**0.37 [0.2-0.8] 0.014**	0.49 [0.2-1.4] 0.189	1.63 [0.4-7.2] 0.523	3.04 [0.3-27.1] 0.319	**0.31 [0.1-0.7] 0.006**	1.11 [0.3-4.1] 0.873
Partner is confidante						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.66 [0.3-1.8] 0.406	1.06 [0.3-3.8] 0.935	3.12 [0.4-24.0] 0.274	2.04 [0.2-16.8] 0.507	**0.22 [0.1-0.5] 0.000**	**0.30 [0.1-0.9] 0.028**
Clinic staff are friendly						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	**0.46 [0.2-0.9] 0.029**	0.55 [0.2-1.3] 0.180	1.80 [0.5-6.1] 0.345	2.30 [0.5-10.5] 0.281	0.58 [0.3-1.3] 0.188	0.63 [0.2-1.8] 0.402
Partner makes life harder						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	**2.87 [1.8-4.5] 0.000**	**2.48 [1.4-4.4] 0.002**	1.01 [0.6-1.7] 0.981	1.07 [0.6-2.0] 0.827	**5.72 [3.4-9.7] 0.000**	**5.92 [3.0-11.8] 0.000**
Community organisation						
Does not attend/ irregularly	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]

Attends regularly	**0.87 [0.6-1.3] 0.523**	1.00 [0.6-1.7] 0.998	0.86 [0.5-1.4] 0.548	0.90 [0.5-1.6] 0.734	0.82 [0.5-1.3] 0.429	0.69 [0.4-1.3] 0.248
Has friend with baby						
No or sees irregularly	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes, sees regularly	1.19 [0.8-1.9] 0.439	1.24 [0.7-2.2] 0.458	1.14 [0.7-1.9] 0.607	1.14 [0.6-2.1] 0.665	1.09 [0.7-1.8] 0.727	0.86 [0.4-1.7] 0.654

* Age and asset score are continuous variables; **Antenatal stressors are continuous scores

Supplementary table 4.4 : Factors associated with anxiety by pattern of onset and recovery across pregnancy

	Early-recover		Late onset		Persistent	
	RR [CI] p	**ARR [CI] p**	**RR [CI] p**	**ARR [CI] p**	**RR [CI] p**	**ARR [CI] p**
Age*	**0.94 [0.9-1.0] 0.010**	0.95 [0.9-1.0] 0.131	1.00 [1.0-1.0] 0.894	1.00 [0.9-1.1] 0.958	**0.93 [0.9-1.0] 0.032**	0.96 [0.9-1.0] 0.300
Education						
Primary/ secondary	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Tertiary/ professional	1.18 [0.7-2.1] 0.574	1.12 [0.5-2.4] 0.761	1.34 [0.8-2.2] 0.265	1.27 [0.7-2.4] 0.468	1.62 [0.8-3.4] 0.203	**2.58 [1.0-6.7] 0.050**
Relationship status						
Single	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Married/ cohabiting	0.70 [0.4-1.2] 0.224	0.71 [0.3-1.5] 0.354	0.98 [0.6-1.6] 0.950	1.10 [0.6-2.0] 0.765	0.57 [0.3-1.3] 0.162	0.79 [0.3-2.1] 0.630
People in household						
≤3	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
≥4	1.37 [0.8-2.4] 0.253	1.04 [0.5-2.1] 0.921	1.16 [0.7-1.9] 0.555	1.36 [0.8-2.4] 0.303	1.31 [0.6-2.7] 0.466	1.07 [0.4-2.6] 0.884
Children < 5 years						
No children < 5 years	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Children <5 years	**2.17 [1.3-3.7] 0.005**	1.68 [0.9-3.3] 0.132	0.85 [0.5-1.4] 0.535	0.55 [0.3-1.0] 0.069	1.20 [0.6-2.5] 0.627	1.59 [0.6-4.0] 0.322
Asset score*	1.18 [1.0-1.4] 0.118	1.25 [0.9-1.6] 0.113	1.00 [0.8-1.2] 0.988	1.00 [0.8-1.3] 0.967	**0.79 [0.7-1.0] 0.019**	0.76 [0.6-1.0] 0.059
Parity						
1st pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
2nd+ pregnancy	0.71 [0.4-1.3] 0.245	1.04 [0.5-2.3] 0.915	1.02 [0.6-1.8] 0.951	1.16 [0.6-2.4] 0.682	**0.38 [0.2-0.8] 0.007**	0.47 [0.2-1.2] 0.102
Reproductive intention						
Unplanned pregnancy	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Planned pregnancy	0.67 [0.4-1.2] 0.157	0.72 [0.4-1.4] 0.334	0.89 [0.6-1.4] 0.646	0.89 [0.5-1.6] 0.696	0.98 [0.5-2.0] 0.952	1.39 [0.6-3.3] 0.445
Smoked (last 3 months)						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1.10 [0.4-2.7] 0.840	1.55 [0.5-4.9] 0.459	0.53 [0.2-1.5] 0.240	0.41 [0.1-1.6] 0.199	1.77 [0.6-4.8] 0.266	0.71 [0.2-2.9] 0.637
Alcohol use						
No alcohol use	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Weekly alcohol use	0.77 [0.3-2.0] 0.599	0.73 [0.2-2.2] 0.580	1.64 [0.8-3.2] 0.147	1.77 [0.8-4.1] 0.179	2.12 [0.9-5.1] 0.095	2.27 [0.7-7.3] 0.170

Mental illness (previous)						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	-	-	**4.86 [1.8-13.5] 0.002**	**4.82 [1.5-16.0] 0.010**	1.56 [0.2-12.7] 0.678	1.53 [0.2-15.6] 0.718
HIV status						
HIV Negative	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
HIV positive	0.96 [0.5-1.7] 0.901	1.10 [0.5-2.2] 0.788	0.70 [0.4-1.2] 0.206	0.65 [0.3-1.3] 0.216	0.94 [0.4-2.0] 0.867	1.49 [0.6-3.8] 0.401
Antenatal stressors**						
Marital stress	1.15 [0.7-2.0] 0.622	0.77 [0.4-1.6] 0.466	0.96 [0.6-1.6] 0.879	0.96 [0.5-1.9] 0.907	1.64 [0.9-3.1] 0.121	1.32 [0.6-3.1] 0.520
Family stress	1.30 [0.9-1.8] 0.104	1.25 [0.8-1.9] 0.257	1.21 [0.9-1.6] 0.191	1.40 [1.0-2.0] 0.065	**1.60 [1.1-2.4] 0.017**	**1.71 [1.1-2.7] 0.027**
Economic stress	1.23 [0.9-1.6] 0.144	1.16 [0.8-1.6] 0.404	1.09 [0.9-1.4] 0.496	0.93 [0.7-1.3] 0.646	1.03 [0.7-1.5] 0.892	0.76 [0.5-1.2] 0.280
Societal stress	1.11 [0.6-2.1] 0.765	0.64 [0.3-1.6] 0.329	1.14 [0.6-2.0] 0.664	0.99 [0.5-2.0] 0.985	1.50 [0.7-3.1] 0.278	1.31 [0.5-3.5] 0.591
Has practical support						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.78 [0.3-2.1] 0.617	0.64 [0.2-2.0] 0.444	0.62 [0.3-1.4] 0.256	0.82 [0.3-2.4] 0.719	**0.32 [0.1-0.8] 0.019**	**0.18 [0.1-0.6] 0.004**
Has confidante						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.48 [0.2-1.2] 0.125	0.49 [0.1-1.7] 0.269	0.54 [0.2-1.3] 0.174	0.59 [0.2-1.9] 0.369	0.53 [0.2-1.9] 0.323	5.50 [0.4-69.4] 0.188
Partner is confidante						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1.05 [0.3-3.6] 0.934	1.42 [0.3-5.8] 0.626	1.03 [0.3-3.1] 0.956	0.92 [0.3-3.3] 0.898	0.40 [0.1-1.2] 0.111	0.44 [0.1-1.8] 0.249
Clinic staff are friendly						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	0.76 [0.3-1.9] 0.561	1.08 [0.3-3.5] 0.891	1.03 [0.4-2.5] 0.952	1.49 [0.5-4.7] 0.500	0.62 [0.2-1.9] 0.401	0.36 [0.1-1.2] 0.108
Partner makes life harder						
No	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes	1.25 [0.7-2.1] 0.427	1.13 [0.6-2.3] 0.722	1.09 [0.7-1.8] 0.714	1.14 [0.6-2.1] 0.667	1.32 [0.7-2.7] 0.434	0.96 [0.4-2.4] 0.927
Community organisation						
Does not attend/ irregularly	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Attends regularly	0.77 [0.4-1.3] 0.334	0.76 [0.4-1.4] 0.404	**0.59 [0.4-0.9] 0.027**	0.62 [0.4-1.1] 0.093	1.12 [0.5-2.3] 0.749	1.08 [0.5-2.6] 0.864

Has friend with baby						
No or sees irregularly	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]	1.00 [1.0-1.0]
Yes, sees regularly	0.99 [0.6-1.7] 0.967	1.07 [0.6-2.1] 0.838	1.07 [0.7-1.8] 0.788	1.35 [0.8-2.4] 0.303	1.17 [0.6-2.4] 0.677	1.59 [0.7-3.8] 0.298

* Age and asset score are continuous variables; **Antenatal stressors are continuous scores

Appendix F: Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Stephanie Elaine Redinger (Student number: 1589572) am a student registered for the degree of Doctor of Philosophy (Paediatrics) in the academic year 2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: SRedinger Date: 25/04/2021

Appendix G: Turn it in report