Trajectories of perinatal depressive symptoms in South Africa

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Declarations

I, Emily Garman, present this thesis in fulfilment of the requirements for the degree of Doctor of Philosophy in the Department of Psychiatry and Mental Health, Faculty of Health Sciences, University of Cape Town. I hereby declare that this thesis is based is my original work and that neither the whole work nor any part of it has been, is being, or will be submitted for another degree in this or any other university. Ethical approval was obtained from Ethics Research Committee of the Faculty of Health Sciences at the University of Cape Town (HREC REF: 835/2015) (see Appendix A).

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the four publications listed below in my PhD thesis. Where co-authorships are involved, the co-authors have agreed that I may include the publications:

1. Baron EC, Bass J, Murray SM, Schneider M, Lund C. (2017). A systematic review of growth curve mixture modelling literature investigating trajectories of perinatal depressive symptoms and associated risk factors. *Journal of Affective Disorders*; 223:194-208.[1]
2. Garman EC, Schneider M, Lund C (2019). Perinatal depressive symptoms among low-income South African women at risk for depression: trajectories and predictors. *BMC Pregnancy and Childbirth*; 19:202.
3. Garman EC, Cois A, Tomlinson M, Rotheram-Borus MJ, Lund C (2019). Course of perinatal depressive symptoms among South African women: associations with child outcomes at 18 and 36 months old. *Social Psychiatry and Psychiatric Epidemiology*; doi: 10.1007/s00127-019-01665-2.
4. Garman EC, Cois A, Schneider M, Lund C (2019). Association between perinatal depressive symptoms and suicidal risk in low-income South African women: a longitudinal study. *Social Psychiatry and Psychiatric Epidemiology;* doi: 10.1007/s00127-019-01730-w.

Please see Appendix B for my letter of motivation to the Doctoral Degrees Board, which describes my contribution to each of the above publications.

[1] **Note that this article was published under my maiden name Baron.**

Note that the abstract for each publication was edited slightly and used as a summary at the beginning of each related Chapter. Similarly, the layout, subheadings and wording of the above publications were edited slightly for the purpose of this thesis and to ensure a consistent format throughout. Finally, the publications included in Chapters 3 and 5 were still under review at the time I submitted my PhD Thesis, and have since then been edited in response to the reviewers comments; edits which are not reflected in the present Thesis. Also, minor corrections were made throughout this Thesis in response to the PhD examiners' comments. Thus, Chapters 2 to 5 are not direct replicas of the publications listed above.

Signature Signed by candidate Date: 18/06/2019

Abstract

Perinatal depression, which occurs during pregnancy and within one year postpartum, is highly prevalent in South Africa. It is associated with greater risk of birth complications, poorer health outcomes and greater risk of suicide behaviours for the mother. Perinatal depression is also associated with poorer physical, cognitive, socio-emotional and behavioural development for her child. There is preliminary evidence using growth curve mixture modelling (GCMM) that the course of perinatal depression is heterogeneous, and that each course is associated with a range of risk factors and child outcomes. Most of this evidence is generated in high-income countries (HICs), however. Little is known about the course of perinatal depression in low-income settings, where women are more likely to experience social and economic adversity, and where the patterns of risk among mothers and their children are likely to differ. The overall aim of this thesis was to identify the trajectories of perinatal depressive symptoms among low-income women in South Africa, and investigate whether these were associated with specific psychosocial and economic risk factors, child outcomes and suicidal risk over time.

First, the available literature on the use of GCMM to identify trajectories of perinatal depressive symptoms is systematically reviewed. Evidence, all from HICs, suggests that there are heterogenous trajectories. The most commonly reported trajectories are (i) a 'low-risk' trajectory, characterised by chronically low levels of depressive symptoms throughout the perinatal period, (ii) a 'high-risk' trajectory, characterised by chronically severe levels of depressive symptoms, and (iii) an 'antenatal' trajectory, with greater levels of symptoms antenatally, which naturally abate before or just after birth. How women with different trajectories differ in terms of social, economic and health-related characteristics was inconsistent.

Data from two randomised controlled trials (RCTs) were then utilised to investigate the trajectories of depressive symptoms among perinatal women living in a low-income setting in South Africa. Both RCTs were conducted in Khayelitsha, a peri-urban township settlement close to Cape Town, characterised by high levels of poverty and unemployment, and high crime rates. The RCTs were the Africa Focus on Intervention Research for Mental Health, and the Philani Intervention Programme. The former was conducted among perinatal women at risk for depression during pregnancy, while the latter was conducted among all perinatal women, regardless of the severity of their depressive symptom at recruitment. No differences were found in depressive symptoms between the control and intervention arms in either RCT, so both arms were combined, where appropriate. The trajectories of

perinatal depressive symptoms, identified though growth mixture modelling or latent class growth analysis, were similar to those reported in the systematic review. A high-risk trajectory was identified in both samples; it was characterised by greater socio-economic and health-related risks, including alcohol use during pregnancy and lower levels of social support, factors which differentiated women allocated to this trajectory from women who had low symptom levels or who showed a natural remission pattern over the perinatal period. Children of mothers with chronically severe depressive symptoms reported greater emotional problems at 36 months postpartum. Children of mothers who reported more severe depressive symptoms either early or later in the postpartum period also showed poorer physical growth at 18 and 36 months. Finally, a series of generalised estimating equations indicated that change in depressive symptoms among women initially at risk for depression during pregnancy was associated with change in the severity of suicidal risk during the perinatal period, but only when depressive symptoms decreased, and that among younger women and those who showed a lower risk trajectory of depressive symptoms.

Relatively similar trajectories of perinatal depressive symptoms were identified among perinatal women in Khayelitsha, compared to studies in HICs. Women presented with different trajectories of depressive symptoms over the perinatal period, each with specific sets of risk factors and distinct associations with severity of suicidal risk and child outcomes over time. Depression and suicidal risk should be assessed independently from one another throughout the perinatal period. The consistently identified high-risk trajectory highlights the need to integrate health, social and economic characteristics into the identification and prevention strategies for perinatal depression. Given the limited mental health resources available at primary care level in South Africa, this thesis contributes to developing efficient methods to identify, refer and manage women who may need more intensive mental health care.

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I would also like to thank the Africa Focus on Intervention Research for Mental Health team at the University of Cape Town (UCT), including Thandi Davies and Memory Munodawafa, as well as the counsellors and fieldworkers, for their wonderful work and dedicated efforts towards the completion of the randomised controlled trial in Khayelitsha. Thank you also to Mark Tomlinson and Mary Jane Rotheram-Borus, who agreed to share the Philani Intervention Programme data, and to Ellen Almirol and Johnny Hossell, who kindly facilitated access and provided support while I familiarised myself with the dataset.

I would also like to acknowledge Dr Sujit Rathod – for his statistical guidance and his irritating but useful approach to capacity building – which, in the end, has contributed to the researcher and statistician I am today. I am also grateful to my supervisors Prof Crick Lund and A/Prof Marguerite Schneider, who provided significant support throughout the years, despite my perfectionism and infamous stubbornness.

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A big thank you to my parents, to whom I owe everything – I would not be where I am if it weren't for their ongoing encouragement, patience, guidance and insight. Thanks to my sister Margaux for her continuous support and bringing me laughter through the hard times. I do apologise to her, however, for falsely advertising the PhD life, as she ventures into her first doctoral year in Lausanne, Switzerland.

And of course, thanks to my amazing husband Russell – for his unwavering support and unconditional love despite the long hours and endless weekends of work; and most of all, for believing in me, even when I didn't.

Table of Contents

List of Abbreviations

AFFIRM	Africa Focus on Intervention Research for Mental Health
AIC	Akaike Information Criterion
aOR	Adjusted odds ratio
AUDIT	Alcohol Use Disorder Identification Test
AUDIT-C	Derived Alcohol Use Disorder Identification Test
BDI	Beck Depression Inventory
BIC	Bayesian Information Criterion
BLRT	Bootstrap Likelihood Ratio test
CBCL	Child Behaviour Checklist
CES-D-20	Centre for Epidemiological Studies – Depression scale
CHW	Community health worker
CI	Confidence intervals
CMD	Common mental disorder
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th edition
EPDS	Edinburgh Postnatal Depression Scale
FAI	Cape Town Functional Assessment Instrument
GCMM	Growth curve mixture model
GEE	Generalised estimating equations
GMM	Growth mixture modelling
HDRS	Hamilton Depression Rating Scale
HFIAS	The Household Food Insecurity Access Scale
HIC	High-income country
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Commission
ICD-11	International Statistical Classification of Diseases and Related Health Problems 11th rev.
IQR	Interquartile range
IPV	Intimate partner violence
KZN	KwaZulu Natal
LCGA	Latent class growth analysis
LMIC	Low- and middle-income country
LMRT	Lo-Mendell-Rubin test
Mdn	Median
mhGAP	Mental Health Gap Action Programme

MINI	Mini International Neuropsychiatric Interview
MOU	Midwife Obstetrics Unit
MSPSS	Multidimensional Scale of Perceived Social Support
NGO	Non-governmental organisation
OR	Odds ratio
PACT	Postpartum Depression: Action Towards Causes and Treatment
PHC	Primary health care
PMTCT	Prevention of Mother-To-Child Transmission
RCT	Randomised controlled trial
SASH	South African Stress and Health
SD	Standard deviation
SDQ	Strengths and Difficulty Questionnaire
US	United States of America
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule

List of Figures

List of Tables

List of Appendices

Chapter 1. Introduction

This Chapter reviews the global and South African literature pertaining to the epidemiology of perinatal depression within an ecological model. It then summarises the current evidence on the heterogeneity in the course of perinatal depressive symptoms, and the implications these have on research investigating risk factors for perinatal depression, its impact on child outcomes and its association with suicidal behaviours. The rationale for this thesis and research objectives are then described, given the South African guidelines for maternity care, the National Mental Health Policy Framework and Strategic Plan, and primary health care re-engineering plan currently in place. Finally, the setting in which the present research took place, and my role within this research are briefly described.

1.1. Defining perinatal depression

According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) (American Psychiatric Association, 2013) and the International Statistical Classification of Diseases and Related Health Problems 11th Revision (ICD-11) (World health Organization, 2018b), a depressive episode is defined as a two-week period characterised by low mood or loss of interest or pleasure, and often accompanied by difficulties concentrating, reduced energy, change in sleep and eating patterns, feelings of worthlessness, psychomotor impairments or suicidal ideation; all of which can affect numerous domains of daily functioning. The criteria are identical for perinatal depression, with an added onset criterion ranging from pregnancy (antenatal depression) to either four weeks postpartum (postnatal depression) in the DSM-V or six weeks postpartum according to the ICD-11. Timing of onset, however, has been debated in the literature, and often extended to 12 weeks postpartum in epidemiological research (Vliegen *et al.*, 2014, Woody *et al.*, 2017). The present research adopts the broader definition used by the World Health Organization (WHO) and considers any depressive episode occurring during pregnancy or up to 12 months postpartum as perinatal depression (World Health Organization, 2010).

1.2. Burden of perinatal depression

Extensive research has been conducted to assess the prevalence of perinatal depression globally. Systematic reviews have generally estimated a greater prevalence in low- and middle-income

countries (LMICs), ranging from 19.0% to 25.3% (Fisher *et al.*, 2012, Gelaye *et al.*, 2016), compared to high-income countries (HICs), where prevalence ranges between 6.5% and 12.8% (O'hara and Swain, 1996, Bennett *et al.*, 2004, Gavin *et al.*, 2005). However, estimates vary greatly across regions, population types, and depending on the diagnostic assessment or screening instruments used. Taking into account this heterogeneity, a recent systematic review and meta-analysis of population-based surveys reported a pooled prevalence of 11.9% for perinatal depression globally (Woody *et al.*, 2017). No difference in the prevalence of antenatal and postnatal depression was found; a surprising finding, given that a previous meta-analyses of common mental disorders (CMD), encompassing both depression and anxiety, reported a 15.6% and 19.8% weighted prevalence of antenatal and postnatal CMD in LMICs, respectively. This lack of difference may be due to a greater heterogeneity in the definitions of postpartum depression used in the studies included in this review: as authors report, some studies use the more stringent DSM-V definition of onset within 4 weeks after birth, while others use a more relaxed definition of up to one year postpartum. In the same review, Woody *et al*. (2017) also report a significant but small difference in prevalence by country income groups, with a prevalence of 13.1% and 11.4% in LMICs and HICs, respectively. The small difference in prevalence may be due to the fact that only population-based surveys or representative samples were included in the review – a criterion absent from previous systematic reviews. This likely decreased the pool of available data from LMICs, where representative population-based or epidemiological studies on perinatal depression are scarce.

In South Africa specifically, evidence on the prevalence of perinatal depression often stems from small clinical samples, which provide a mixed picture. Using the Mini International Neuropsychiatric Interview (MINI) 6.0 (Sheehan *et al.*, 1998), van Heyningen *et al.* (2016) reported a prevalence of antenatal depression of 22% among pregnant women attending their first antenatal visit at a midwife obstetric unit in Hanover Park, a peri-urban settlement of Cape Town. Another clinic-based study in a high HIV-prevalent rural area in KwaZulu Natal (KZN) reported that 39% of pregnant women met the criteria for major depressive disorder (Rochat *et al.*, 2013a). A greater prevalence is often reported in other community and clinic-based studies which make use of screening instruments, such as the Edinburgh Postnatal Depression Scale (EPDS; (Cox *et al.*, 1987)), rather than diagnostic assessments to identify women at high risk for antenatal depression. They report that between 21% to 39% of pregnant women screened above the instruments' clinical threshold (Hartley *et al.*, 2011, Manikkam and Burns, 2012, Brittain *et al.*, 2015, Groves *et al.*, 2015, Tomlinson *et al.*, 2015a, Redinger *et al.*, 2017). Most studies included samples that were representative of pregnant women attending the antenatal care facilities, so the heterogeneity in prevalence of antenatal depression is likely to be due to differences in the sensitivity of the screening tools used. An even greater prevalence was reported

in a study conducted among a high-risk group of rural HIV-positive women, where 49% screened positive on the EPDS. Fewer studies have investigated the prevalence of postnatal depression in South Africa. Two studies reported that 24% (Verkuijl *et al.*, 2014) and 32% (Dewing *et al.*, 2013) of women were at high risk for postnatal depression, based on the Centre for Epidemiological Studies Depression Scale (Radloff, 1977) and the EPDS, respectively. In Cooper *et al.* (1999)'s older study conducted in Khayelitsha, another peri-urban township settlement in Cape Town, 35% of postnatal women were diagnosed with depression. Despite the range of prevalence reported for both antenatal and postnatal depression in South Africa, these are often greater than those reported in other LMICs in Sub-Saharan Africa*;* perhaps due to the post-Apartheid legacy of high inequality, systematic racial discrimination, high rates of gender-based violence and high HIV prevalence.

According to the 2017 estimates of global burden of disease, depressive disorders account for 2.3% of the disability-adjusted life years among women globally (Kyu *et al.*, 2018). The high comorbidity of depression with other physical and chronic diseases, including HIV/AIDS and tuberculosis, is one of the reasons why depressive disorders are the fifth leading cause of years lived with disability in South Africa (Institute for Health Metrics and Evaluation, 2017), where 21.2% of women aged 15-49 years are HIV positive (UNAIDS, 2017). Women suffering from antenatal depression are also at greater risk of miscarriage, pre-term delivery, and at greater risk of experiencing birth complications, such as haemorrhage during birth, prolonged labour or caesarean-section delivery (Lusskin *et al.*, 2007a, Hanlon *et al.*, 2009, Gelaye *et al.*, 2016).

1.2.1. Perinatal depression and suicidal behaviours

In perinatal and non-perinatal populations, depression also often co-occurs with suicidal behaviours. In line with a recent definition proposed by Silverman *et al.* (2007), suicide is defined here as a suicidal attempt that resulted in death, whereas suicidal behaviours, which comprise thoughts, plans or attempts, refer to non-fatal behaviours with suicidal intent. This definition excludes deliberate self-harm, which refers to repetitive bodily harm without suicidal intent. According to the World Health Organization (WHO), the estimated global mortality rate due to suicide is 10.6 per 100,000 individuals, an increase of 60% in the past 45 years (World Health Organization, 2018a). It is estimated that 79% of suicides occur in LMICs (World Health Organization, 2018a), where suicide remains the leading cause of deaths among 15- to 19-year old women (Petroni *et al.*, 2015). Non-fatal attempts, which also bear important economic costs to society (World Health Organization, 2014b, Bantjes *et al.*, 2016), are twenty times more common than suicides, globally (Silverman *et al.*, 2007).

In South Africa, the mean annual estimates of suicide are between 10.9 to 32.5 per 100,000 (Mars *et al.*, 2014), with a male to female ratio of 5:1 (Burrows and Laflamme, 2006), reflecting global tendencies (Bachmann, 2018). Results from the South African Stress and Health (SASH) study, a 2002 to 2004 survey among a representative sample of South African adults, indicated that the lifetime prevalence of suicide attempts, plans and ideation was 2.9%, 3.8% and 9.1%, respectively (Joe *et al.*, 2008). Women also reported twice as many attempts as men (3.8% vs. 1.8%), in line with African literature (Mars *et al.*, 2014).

Evidence suggests that the prevalence of suicides may be lower among the perinatal population specifically, compared to the general female population globally (Lindahl *et al.*, 2005). According to Lindahl *et al.* (2005), this may be due to the increased support and access to health care services women receive during that specific period. In a recent review on maternal deaths in LMICs, however, no differences were found in the prevalence of suicides among the perinatal and non-perinatal population of reproductive age in Africa specifically (Fuhr *et al.*, 2014). In their review, Fuhr *et al.* (2014) adjusted estimates of deaths by suicide by taking into account deaths by injury, on account that suicides are often underreported and until recently, were neither considered direct or indirect obstetric-related deaths, nor coincidental deaths. The review's results also indicated that, on average, 1% of maternal deaths were attributed to suicide. In South Africa, suicides also accounted for 1% of maternal deaths between 2014 and 2016, according to the National Committee for Confidential Enquiries into Maternal Deaths (2018).

The prevalence of non-fatal suicidal behaviours is much higher among the perinatal population, however. A global review revealed that between 5% and 14% of women reported suicidal ideation during pregnancy or the postpartum period (Lindahl *et al.*, 2005). In Onah *et al.* (2017)'s study of South African pregnant women attending their first antenatal visit in Hanover Park in Cape Town, 18% reported suicidal ideation or plan using the MINI interview. Over a quarter (27.5%) endorsed the suicide/self-harm ideation item on the EPDS in Rochat *et al.* (2013a)'s study of pregnant women in KZN. In the latter study, women reported that suicide was a way to cope with an 'insurmountable' problem or situation., which supports global evidence suggesting suicide is seen as a solution or way out (Bantjes *et al.*, 2016).

An association between depression or greater depressive symptoms and an increased risk of suicidal behaviours has systematically been reported among South African perinatal samples (Dewing *et al.*, 2013, Rochat *et al.*, 2013a, Onah *et al.*, 2017). This supports previous international literature suggesting that depression is the most common mental disorder among those who commit suicide

(Turecki and Brent, 2016). However, evidence also indicates that while depression is a strong risk factor for suicidal behaviours (Mars *et al.*, 2014), such behaviours can also occur in the absence of any mental illness, and that the association between depression and suicide plans or attempts is often mediated by suicidal ideation (Nock *et al.*, 2009). Similarly in South Africa, Rochat *et al.* (2013a) report that 10% of pregnant women who reported ideation of suicide or self-harm were not depressed. In Onah *et al.* (2017)'s study, the proportion of pregnant women who were not depressed among those who reported suicidal behaviours was much greater (67%), even though women who were diagnosed with depression were nearly twice as likely to report suicidal behaviours compared to non-depressed women. So, while suicidal behaviours contribute to the burden of perinatal depression, evidence suggests that suicidal behaviours may be present during the perinatal period even in the absence of depression. Even if not fatal, suicidal behaviours can affect the mother and her child's health (Lindahl *et al.*, 2005, Gentile, 2011).

1.2.2. Perinatal depression and child development

Even in the absence of suicidal behaviours, perinatal depression can have direct detrimental effects on child development, thus perpetuating the burden of perinatal depression to the next generation. Extensive research has been conducted in the field of child development with a view to preventing the debilitating effects of both antenatal and postnatal depression on child physical, cognitive, socio-emotional and behavioural development. The aetiology of impaired child development is likely to be a complex one, influenced by the interaction of multiple biological, social and environmental risk factors (Stein *et al.*, 2014, Liu *et al.*, 2017). Several mechanisms have been suggested to explain the role of antenatal depression in relation to adverse child outcomes; these include foetal programming, genetic influences and gene-environment interactions, as well as hormonal or biological influences, especially in relation to intrauterine cortisol levels and HPA axis development (Herba *et al.*, 2016). Maternal undernutrition and poor self-care have also been proposed as a potential mechanism (Parsons *et al.*, 2015). Postnatal depression, on the other hand, is thought to impact child development through parents' cognitive and parenting styles, family conflict, social support, as well as the child's temperament and social skills (Goodman and Gotlib, 1999, Ahun *et al.*, 2017).

The majority of the evidence supporting these pathways originates from studies conducted in HICs, most of which indicate that children who are exposed to postnatal maternal depression are more likely to present internalising and externalising behaviour problems (Goodman *et al.*, 2011) – measures often used as a proxy for mental health problems among children (Herba *et al.*, 2016). A more recent meta-analysis also reported that both antenatal and postnatal depression had an impact

on cognitive development among children aged up to seven years. The same findings were reported when only longitudinal studies were included (Liu *et al.*, 2017); an important finding given that the majority of the literature in both HICs and LMICs is based on cross-sectional evidence.

Evidence of the association between perinatal depression and child development is limited but growing in LMICs. In Gelaye *et al.* (2016)'s review of the literature, evidence pointed to both antenatal and postnatal depression having an effect on children's attachment style, social development, motor development and behavioural problems. For example, greater externalising problems were found among two-year old children of mothers who had been at risk for depression at six months postpartum in a South African birth cohort study in Johannesburg (Avan *et al.*, 2010). A follow-up study among the same cohort showed that externalising problems persisted when children were 10 years of age, controlling for concurrent maternal depressive symptoms (Verkuijl *et al.*, 2014). Also, Tomlinson *et al.* (2006) found that mothers living in Khayelitsha who suffered from postnatal depression two months after giving birth were more likely to develop insecure attachment styles with their infants. However, in a study conducted in the same area among HIV-positive women, 10 to 12 months after giving birth, no association was found between above-threshold postnatal depressive symptoms and infants' social withdrawal, known to reflect internalising problems (Hartley *et al.*, 2011).

In LMICs, more research has focused on the impact of perinatal depression on physical health outcomes, perhaps because growth and malnutrition remain the leading causes of under 5-mortality rates in LMICs (Black *et al.*, 2010, Walker *et al.*, 2012). In South Africa, for example, the overall under-5 mortality rate is 42 deaths per 1000 live births (Department of Health, 2017), with intestinal infectious diseases and malnutrition as the second and fourth leading causes of death, respectively (Statistics South Africa, 2017b). Also, two thirds of South African children who die within one year postpartum are malnourished, 35% of whom are severely malnourished (National Department of Health, 2012). Evidence from studies conducted in LMICs in South Asia suggests there is an increased risk for low birthweight and intrauterine growth restriction among newborns of mothers suffering from depression during pregnancy (Patel and Prince, 2006, Rahman and Creed, 2007). Two other studies conducted in Pakistan also reported that antenatal depression predicted poor growth in infants up to 12 months postpartum (Rahman *et al.*, 2004) and that postnatal depression increased the children's risk of diarrhoeal diseases (Rahman *et al.*, 2007). Evidence of the impact of perinatal depression on child growth is mixed in Sub-Saharan Africa (Gelaye *et al.*, 2016, Surkan *et al.*, 2016) and in South Africa, however. For example, results from a birth cohort study conducted in the Western Cape in South Africa indicated that infants of women at risk for antenatal depression at 20 to 28 weeks gestation, were more likely to have lower weight-for-age and head circumference-for-age z-scores at

birth (Brittain *et al.*, 2015). Yet Tomlinson *et al.* (2006) found no association between postnatal depression and child growth at 2 months or 18 months postpartum.

Altogether, there is compelling evidence from LMICs on the high prevalence of perinatal depression and its burden, both in terms of maternal physical health, mortality and morbidity through suicidal risk and in terms of child poor growth, and cognitive and socio-emotional development. Poor growth is also a key indicator of children's health and nutritional status (Parsons *et al.*, 2012), which is in turn associated with poorer cognitive and physical outcomes later in adulthood (Swamy and SkjŠrven, 2008, World Health Organization, 2009), and associated with reduced economic productivity (Haas *et al.*, 1996, Victora *et al.*, 2008, Dewey and Begum, 2011). It is therefore essential to identify which and when women are most at risk for developing perinatal depression so that prevention and treatment strategies can be developed and the health, disability and economic burden of perinatal depression on women and children can be reduced.

1.3. Risk factors for perinatal depression

To that effect, extensive research has been conducted to document the risk factors for antenatal and postnatal depression. The ecological model provides a good framework for understanding how risk and protective factors influence the mental health of pregnant and postnatal women in LMICs (Petersen *et al.*, 2010). According to this model, which follows from Bronfenbrenner (1994)'s ecological developmental perspective, risk and protective factors operate at different levels of an individual's ecosystem (see Figure 1.1): proximal influences can occur at the individual level (e.g. genetic influences, temperament, personality), interpersonal level (immediate social factors, such as family, colleagues) or at community level (social connectedness, social capital), and distal influences operate at the structural societal level (economic policies, cultural influences). As such, individuals' mental health cannot be separated from social, community and structural influences. In South Africa, this means that the post-Apartheid legacy of inequality, conflict and violence must be taken into account when investigating the risk factors for mental illness, and perinatal depression more specifically.

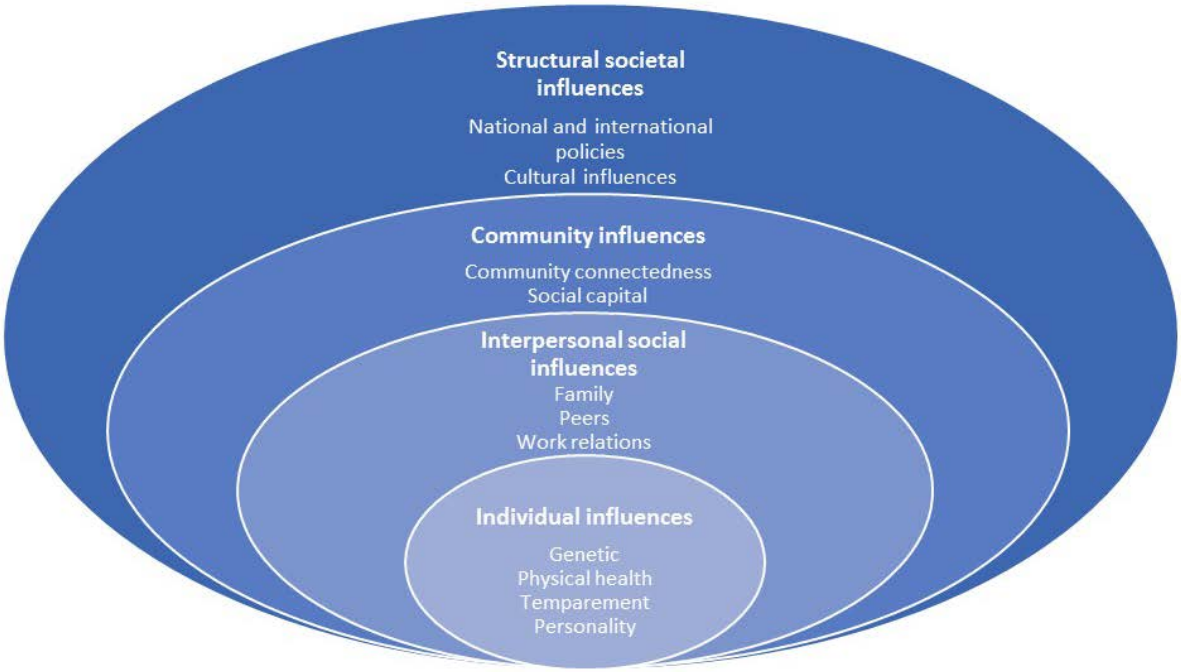

Figure 1.1 Levels of risk and protective influences for mental health

In South Africa, 21% of the population lives under extreme poverty (Budlender *et al.*, 2015) and 38% of households report food insufficiency (Sorsdahl *et al.*, 2011). Similarly to what global evidence suggests (Sawyer *et al.*, 2010, Fisher *et al.*, 2012, Biaggi *et al.*, 2016), evidence on the association between low socio-economic status and perinatal depression in South Africa is mixed (Hartley *et al.*, 2011, Brittain *et al.*, 2015, van Heyningen *et al.*, 2016, Redinger *et al.*, 2017). Some studies, however, have investigated the role of food insecurity as a risk factor for perinatal depression, rather than socio-economic status per se. Associations between perinatal depression and food insecurity have been reported among pregnant women in Hanover Park (van Heyningen *et al.*, 2016) and among postnatal women in Khayelitsha, where 60% of the sample reported being severely food insecure (Dewing *et al.*, 2013). In the same area of Khayelitsha, Tsai *et al.* (2012) also reported that food insecurity among pregnant women was a risk factor for postnatal depressive symptoms. This effect, however, was buffered when social support, particularly instrumental support, was taken into account. Indeed, instrumental and emotional support from partners and families are more proximal interpersonal influences which have often been found to be protective factors for perinatal depression, often mitigating the adverse effects of other risk factors within the same or different levels of the individual's ecosystem (Pilkington *et al.*, 2015, Biaggi *et al.*, 2016). Conversely, lack of partner and family support have consistently been associated with antenatal and postnatal depressive symptoms in South Africa (Hartley *et al.*, 2011, Groves *et al.*, 2015, van Heyningen *et al.*, 2016, Redinger *et al.*, 2017), supporting global evidence (Sawyer *et al.*, 2010, Fisher *et al.*, 2012, Biaggi *et al.*, 2016).

According to the social causation pathway hypothesis of the 'negative cycle of poverty', persons living in poverty are more likely to experience heightened stress, violence, trauma, social exclusion and malnutrition, which in turn increases the risk of mental illness (Lund *et al.*, 2010). There is some evidence that women living in low-income settings in South Africa are more likely to experience traumatic events (Seedat *et al.*, 2009a), such as intimate partner violence (IPV), child abuse, disaster or death of a loved one. IPV is, in fact, commonly experienced among South African perinatal women, though the prevalence varies widely across locations and type of IPV investigated. For example, a recent study in an urban sample of pregnant women in KZN reported that 25% were experiencing any form of IPV, though psychological IPV was the most common form and was reported by 20% of the sample (Groves *et al.*, 2015). A smaller proportion (13.9%) of pregnant women living in Khayelitsha and who screened positive on the EPDS reported experiencing either physical or sexual IPV (Schneider *et al.*, 2018). In another study conducted in Soweto, an urban area of Johannesburg, 'only' 7% of pregnant women in their first trimester reported being beaten by their partner. The low prevalence reported in this study is likely due to the exclusion of emotional or sexual violence in the authors' investigation of IPV. Cross-sectional evidence suggests that depressive symptoms during pregnancy are associated with physical IPV (Hartley *et al.*, 2011, Brittain *et al.*, 2015, Peltzer *et al.*, 2016), as well as psychological and sexual IPV (Brittain *et al.*, 2015, Groves *et al.*, 2015). Only Redinger *et al.* (2017) reported that IPV was not associated with antenatal depressive symptoms during the first trimester, once social support was adjusted for. However, in a population-based longitudinal study, Tsai *et al.* (2016) investigated physical IPV during pregnancy in relation to depressive symptoms reported a year later; authors report that the relationship was bidirectional, in that IPV increased the risk of later depression, but that depression during pregnancy also increased the chances of experiencing IPV the following year, as women who were depressed were more likely to remain in harmful relationships.

Other proximal, individual influences reported as risk factors for perinatal depression include alcohol use during pregnancy and HIV. The rates of alcohol consumption per capita are very high in South Africa (World Health Organization, 2014a) and particularly in the Western Cape, including among pregnant women. For example, evidence from a study conducted in Khayelitsha suggests that 8.3% of women still consumed alcohol at 8 months gestation, and 7.1% reported problematic drinking (Davis *et al.*, 2017). Another study conducted in the same area reported hazardous drinking among 16% of women at three months postpartum (Dewing *et al.*, 2013). The adverse effects of alcohol use during pregnancy can be seen through the high rates of Foetal Alcohol Syndrome reported in South Africa, as high as 59.3 to 91.0 per 1000 in the Western Cape (Viljoen *et al.*, 2005, May *et al.*, 2013). Because of the high consumption of alcohol among perinatal women in the area, many studies have investigated the role of alcohol use in the development of perinatal depression among low-income women living

near Cape Town. For example, Davis *et al.* (2017) investigated patterns of alcohol use from pregnancy to five years postpartum among women living in Khayelitsha. They found that alcohol use was only associated with depression six months after birth, but not at later time points. The authors suggest that other factors, such as food insecurity and lack of partner support, may be particularly distressing during the perinatal period, specifically, and therefore may lead to more drinking. In line with this argument, Tomlinson *et al.* (2013) reported on the co-occurrence of risk factors, including depressive symptoms, HIV status and alcohol use among a sample of pregnant women, also living in Khayelitsha. Women who were HIV-positive or who reported drinking during pregnancy were more likely to screen positive on the EPDS. Other more recent studies conducted in other regions of South Africa do not report an association between HIV status and antenatal depression, however (Manikkam and Burns, 2012, Peltzer *et al.*, 2016, Redinger *et al.*, 2017). This could be due to the 'normalisation' of a HIV positive status, which is no longer considered a death sentence now that antiretrovirals are readily available (HIV/AIDS, 2016). Interestingly, HIV has been reported as a risk factor for suicide attempts in a review of the African literature (Mars *et al.*, 2014). In South Africa specifically, where 98% of women get tested for HIV during pregnancy (UNAIDS, 2014), finding out about a positive-HIV status during that period has been reported as a potential trigger for suicidal behaviours (Rochat *et al.*, 2013a).

Evidence from LMICs and South Africa is therefore mixed with regards to risk factors for perinatal depression. It seems food insecurity may be more important as a distal factor than SES in identifying perinatal women at risk for depression. Other proximal risk factors identified in the literature include lack of support, IPV and alcohol use, though findings are still mixed in relation to the role of HIV status in South Africa. The heterogeneous findings on the prevalence of perinatal depression within South Africa, and the mixed findings relating to risk factors and child outcomes associated with perinatal depression highlights the complex nature of perinatal depression. Indeed, recent evidence indicates that perinatal depression, like depression among the general population, is not a homogeneous disorder (Nandi *et al.*, 2009) and is characterised by different profiles and prognoses over time, each associated with different risk factors and implications on child development.

1.4. Heterogeneity in the course of perinatal depression

Antenatal depression has consistently been reported as one of the strongest risk factors for postnatal depression globally (Norhayati *et al.*, 2015). And yet, many women with postnatal depression report not having had any symptoms during pregnancy, while others experiencing antenatal depression report no symptoms after birth (Stowe and Nemeroff, 1995, Gavin *et al.*, 2005). Longitudinal studies also report varied rates of depressive symptoms over the course of the perinatal period, with some

reporting an increase during pregnancy (Da Costa *et al.*, 1999) and others reporting a U-shape curve (Lee *et al.*, 2007). Indeed, a study among pregnant women in Hong Kong showed that the proportion of women showing severe depressive symptoms decreased temporarily during the second trimester (Lee *et al.*, 2007), and that risk factors for severe depressive symptoms differed depending on trimesters, suggesting possibly different profiles of depression during pregnancy. However, in a cohort study conducted in the UK, Evans *et al.* (2001) reported the opposite finding, with the most severe depressive symptoms being reported between 18 and 32 weeks gestation. In the postpartum period, several studies suggest that postnatal depressive symptoms decline naturally by six months postpartum (Vliegen *et al.*, 2014, Prenoveau *et al.*, 2017), while others indicate that symptoms persist beyond one year postpartum (Vliegen *et al.*, 2014, Netsi *et al.*, 2018). Vliegen *et al.* (2014) recently conducted a systematic review of longitudinal studies on the course of postnatal depression. Their results indicate that, when symptom chronicity is taken into account, two trajectories are often reported – one chronic and one remittent. When both chronicity and severity are considered, however, studies most often report, among those with initially severe symptoms, a course of chronic major depression, one of chronic minor depression, and a recurrent major depression course, which never shows full recovery.

In recent years, the notion of chronicity and severity of depressive symptoms during the perinatal period has also been taken into account when assessing the effects of perinatal depression on child development. Until then, the assumption of cross-sectional or longitudinal studies was that any perinatal period during which depressive symptoms predicted poorer child outcomes was considered 'sensitive' for child development (Kingston *et al.*, 2012, Stein *et al.*, 2014). While there is convincing evidence that there may be phases in children's development during which they may be more sensitive to the severity of their mother's depressive symptoms (Dawson *et al.*, 2000, Sohr-Preston and Scaramella, 2006), there is growing evidence that chronicity of such symptoms is also key in understanding the pathways between perinatal depression and child outcomes (Stein *et al.*, 2014). For example, a study among Brazilian mothers showed that the impact of postnatal depression on language development among 12 months old infants increased when the duration of the episode increased (Quevedo *et al.*, 2012). The greater impact of chronic, versus transient, depressive symptoms on child growth and health was also demonstrated in a study conducted in Pakistan, where the risk of underweight, stunting and episodes of diarrhoea was increased among children of mothers screening positive on a depression tool at two months, six months and 12 months postpartum, compared to children of mothers who were at risk for depression at only one or two occasions (Rahman *et al.*, 2004). Similarly, a study among Latina women in the United States (US) indicated that children of mothers who reported severe depressive symptoms both antenatally and at four to six

weeks postpartum were more likely to be underweight at two years old, compared to children of mothers with more transient or no symptoms (Wojcicki *et al.*, 2011).

However, in such studies, the chronicity of depression is often measured as the number of times women screen consecutively above a clinical cut-off on a depression instrument over the course of a study. This is not ideal for several reasons. First, cut-offs on screening instruments are sometimes arbitrary and are likely to vary across populations (Prince, 2008). Second, such cut-offs underestimate the effect of chronic sub-clinical symptoms on the mother's functioning and her child's development, which have been shown to be similar to that of more severe, chronic symptoms (Sohr-Preston and Scaramella, 2006). Finally, because severe episodes are more likely to last longer, it has been argued that chronicity is confounded by severity (Pettit *et al.*, 2009, Prenoveau *et al.*, 2017). Instead, researchers have called for more person-centred approaches to investigate the course of perinatal depression (Vänskä *et al.*, 2011, Vliegen *et al.*, 2014), especially given the major biological, social and psychological changes that pregnancy and the transition to motherhood entail (Bergman and Magnusson, 1997).

1.4.1. Perinatal depressive symptoms and growth curve mixture modelling

An alternative, more complex person-centred analytical approach has recently been used by researchers to assess the course of perinatal depressive symptoms. It combines growth curves with latent class approaches, and is often referred to as growth curve mixture models (GCMM) (Leiby, 2012) or latent variable mixture modelling (Berlin *et al.*, 2014). Such models allow investigators to create latent groups of individuals who have a similar course of symptom severity over time. With this approach, the groups of individuals with different trajectories are not pre-defined, the dichotomisation of clinical vs sub-clinical levels of depressive symptoms is avoided, and the notion of severity and chronicity are not confounded. More information about this analytical method is provided in Chapter 2.

So far, evidence using GCMM mostly comes from HICs and suggests that the course of depressive symptoms can vary widely during the perinatal period, and that each course is often predicted by different risk factors. It is less clear, however, if these risk factors systematically differentiate women with chronic symptom trajectories from those with more transient trajectories. For example, Mora *et al.* (2009) investigated symptoms of depression, using the Center for Epidemiologic Studies – Depression Scale (Radloff, 1977), in a sample of over 1700 low-income women in the US, from their first antenatal visit to two years postpartum (Mora *et al.*, 2009). With the use of growth mixture

modelling (GMM), they identified five trajectories of depressive symptoms: symptoms never presented, antenatal only symptoms, postnatal only symptoms, chronic antenatal and postnatal symptoms, and late postnatal symptoms. Compared to women who never reported symptoms throughout the study, women belonging to more severe trajectory classes reported different demographic, health and psychosocial characteristics, such as a lower education, multiparity, anxiety about the pregnancy, alcohol use and lower self-rated emotional health.

Using the same screening tool for depressive symptoms, (Sutter-Dallay *et al.*, 2012b) used a semiparametric mixture model, similar to GMM, to investigate the course of depressive symptoms among a smaller sample of 550 low-risk women from the third trimester to two years postpartum (Sutter-Dallay *et al.*, 2012a). They reported four trajectories of depressive symptoms: 'clinical symptoms never presented', 'symptoms postnatally', 'symptoms throughout but higher during pregnancy', and 'stable intense symptoms throughout'. Socioeconomic characteristics differentiated women with different symptom trajectories. For example, women with greater depressive symptoms during pregnancy were older, reported lower income and greater trait anxiety compared to those who never experienced symptoms.

Finally, a group of 805 Finnish pregnant women who had just undergone fertility treatment were assessed during their second trimester, and then again at two and 12 months postpartum (Vänskä *et al.*, 2011). With the use of GMM, Vänskä *et al.* (2011) identified five trajectories: a stable trajectory with low symptoms; three transient trajectories, characterised by either severe antenatal only symptoms, or by early or late postnatal only symptoms; and a last trajectory which consisted of heterogeneously high levels of symptoms. Women allocated to the antenatal and early postnatal trajectories were more likely to be multiparous, but no other risk factors were identified, however.

Altogether, these studies indicate that pregnant women with either initially low or high levels of depressive symptoms can show very different patterns of symptom severity over the course of the perinatal period. Emerging evidence also suggests that risk factors may differ across trajectories. These can be useful to differentiate women who report chronically severe symptoms from those whose symptoms remit naturally without any intervention, as well as to differentiate low-risk women from those whose symptoms only worsen in the postpartum period.

1.4.2. Implications for child outcomes

There is also growing evidence that different symptom trajectories are associated with a variety of adverse child outcomes. Vänskä *et al.* (2011)'s study is one of few studies which assessed differences in child outcomes in relation to different latent trajectories. No differences were found in externalising symptoms, social development or perception of language across children aged seven to eight years. They did report, however, that children of mothers allocated to the heterogeneous severe trajectory were more likely to report internalising problems, have worse memory and executive function compared to children of mothers with transient or no symptoms throughout the perinatal period. This supports the idea that timing of severe symptoms may be less important than the chronicity of symptoms in predicting child development problems. Another study assessed maternal depressive symptoms from pregnancy to five years postpartum and found that emotional and behavioural problems were worse among five year-old children of mothers classified in the chronically severe and chronically moderate trajectories (van der Waerden *et al.*, 2015). This corroborates findings from a study in Brazil, where similar internalising and externalising problems were identified among seven-year-old children whose mothers showed either severe or moderate but chronic depressive symptoms from three months to five years postpartum (Matijasevich *et al.*, 2015) compared to children of mothers who reported no depressive symptoms. Both studies indicate that chronic symptoms, even if subclinical, can have adverse effects on child development. They further highlight the importance of moving away from dichotomising depressive symptoms or pre-defining severity and chronicity groups and highlight the need to use less restrictive methods of analyses.

1.4.3. Implications for suicidal risk

The heterogeneity in trajectories of perinatal depressive symptoms should also be considered when assessing the association between perinatal depression and suicidal risk. Until recently, suicidal risk was defined as a linear concept, with risk progressing from ideation, to plan and then to attempt (Turecki and Brent, 2016). More recently, suicidal risk has been conceptualised as cyclical, which has led to an increase in studies investigating the longitudinal patterns of suicidal risk as a continuous phenomenon (Prinstein *et al.*, 2008, Bantjes *et al.*, 2016, Goldston *et al.*, 2016, Kasckow *et al.*, 2016). Goldston *et al.* (2016), for example, considered suicidal behaviours on a spectrum of severity, explaining that, even if brief, one must have thought about and planned suicide before attempting suicide. Based on this premise, they used growth mixture modelling to identify four different trajectories of suicidal risk among individuals recruited during adolescence and followed-up for an average of 14 years. Individuals allocated to either increasing or highest risk trajectories showed

similar patterns of trauma, anxiety, impulsivity and aggression, and lower survival and coping beliefs compared to individuals allocated to the decreasing and low-risk trajectories. Other studies have also used latent modelling to identify change in suicidal risk among diverse populations in HICs (Prinstein *et al.*, 2008, Kasckow *et al.*, 2016, Madsen *et al.*, 2016). While this technique may be simplistic given the complex nature of suicidal risk and its aetiology, it is believed that identifying trajectories can help with understanding and predicting suicidal outcomes.

There is preliminary evidence on the longitudinal association between depression and suicide among the general population. For example, a decline in suicidal ideation was preceded by a decline in depressive symptoms among patients with major depressive symptoms in Finland (Sokero *et al.*, 2006). Also, Miller *et al.* (2017) used a within-person approach to assess the association between change in depression score in relation to increased risk of reporting suicide thoughts or plans among American adolescent girls. While average levels of depressive symptoms were associated with suicidal behaviours, suicidal behaviours were associated with within-person variation in depressive symptoms, but only when adolescents had experienced past abuse. However, to the best of my knowledge, all studies on suicidal behaviours among perinatal women in South Africa have been cross-sectional. While these have been useful in identifying subgroups of perinatal women who are at greater risk of committing suicide, it remains unclear how the course of both perinatal depression and suicide are associated over time, or how the severity and chronicity of depression predicts change in suicidal risk.

Gaining a better understanding of the risk profiles of women who present different trajectories of depressive symptoms, and the trajectories' association with suicidal risk over time has direct clinical implications on how to identify and manage perinatal women at risk for depression or suicide. Also, gaining a better understanding of the impact of symptom severity and chronicity on child development is important in the identification and management of children at risk for impaired growth and development problems, and in the timely implementation of targeted interventions to minimise the time children spend being exposed to their mothers' depressive symptoms. The paucity of research in this field in LMICs is also alarming. More research is needed in low-income settings, where the course of perinatal depressive symptoms and the patterns of risk and resilience among mothers and their children are likely to differ from HICs. This is especially relevant in low-income settings in South Africa, given the levels of poverty and food insecurity, high prevalence of depression, alcohol use during pregnancy, and the high rates of HIV and IPV among the female population of child bearing age. The risk of illness among children is also greater in LMICs (Parsons *et al.*, 2012) and feeding and caregiving practices different from HICs (Surkan *et al.*, 2011); both are likely to affect the relationship between perinatal depression and child development in LMICs.

1.5. Mental health treatment gap for perinatal women

In South Africa, there are currently no formal screening or treatment systems in place to identify, refer and treat women with CMDs, so the majority of women suffering from perinatal depression are most likely not receiving the treatment they need – this is what is commonly referred to as the mental health treatment gap (Saxena *et al.*, 2007). There are no population-based estimates of the treatment gap for perinatal depression in South Africa. Only 28% of South African women diagnosed with a mood disorder reported receiving any form of care in the previous year, according to the 2002 population-based SASH survey (Seedat *et al.*, 2009b).

Unfortunately, the mental health treatment gap is a global phenomenon, and is especially pronounced in LMICs. The contact and effectiveness coverage of individuals with a diagnosis of depression were reported in a recent review of population surveys in 21 countries (Thornicroft *et al.*, 2017). The review indicated that, overall, 56.7% of individuals with a diagnosis of depression recognised the need for help; among these, 71.7% sought care and 16.5% received effective treatment. In contrast, when only LMICs were considered, only 34.6% of individuals with depression recognised the need for care; among these, 52.6% accessed care and 3.7% received effective treatment. The first Lancet series on mental health, published in 2007, helped bring the mental health treatment gap into the forefront of the global health agenda, by calling for action the scaling up mental health services (Chisholm *et al.*, 2007). In the same year, the Movement for Global Mental Health was established, with the aim of increasing treatment coverage for mental disorders in LMICs.

To achieve this, the task-sharing approach (sometimes referred to as task-shifting) has been advocated as a way to integrate mental health services for mental, neurological and substance use disorders into primary health care, a strategy adopted by the WHO's Mental Health Gap Action Programme (mhGAP) initiative (World Health Organization, 2008b). Task-sharing entails making use of non-specialist health workers to provide mental health care under the training and supervision of mental health specialists (Petersen and Lund, 2011, Patel *et al.*, 2013). This has been proposed as the most sustainable way to overcome the lack of mental health professionals available in LMICs (Patel *et al.*, 2011). Also, providing mental health care at primary care level means that it is more accessible, given the comorbidity of mental with physical illnesses, and less stigmatising.

Applying a task-sharing strategy would involve shifting away from diagnosing individuals with a mental illness by mental health professionals, and instead involve using screening instruments by PHC workers to identify individuals who may be at risk for having a mental illness, based on the severity of

symptoms reported (World Health Organization, 2011). Providing that there are referral mechanisms in place to mental health services at primary health care or community level, such screening procedures should help improve detection of individuals who need mental health care (Gilbody *et al.*, 2008, Kagee *et al.*, 2013). Evidence also indicates that psychosocial therapies lend themselves well to task-shared approaches. Such psychosocial treatments, most often developed in HICs, are usually structured approaches to reduce psychological distress or promote adaptive functioning (Leis *et al.*, 2009), and incorporate psychological methods such as cognitive behaviour therapy, interpersonal therapy, problem-solving therapy and psycho-education. These have had to be adapted for low-income settings to improve their acceptability and to address practical barriers, such as low literacy or lack of trained mental health providers. Such adaptations usually involve variations in language, dimensions of concepts, and methods used to provide the intervention (Chowdhary *et al.*, 2013). In their review of adapted psychological interventions for depression among the general population, Chowdhary *et al.* (2013) conclude that, without altering the core theoretical concepts of the original psychological interventions, these interventions can be effective in different cultural populations. This supports an earlier review of trials investigating the effectiveness of psychological therapies for depression and anxiety in low-resource settings, where authors added that cognitive behaviour therapy was slightly more effective, compared to counselling, interpersonal psychotherapy and psychoanalysis (van t'Hof, Cuijpers, Waheed, & Stein, 2011). Since then, additional systematic reviews have reported the effectiveness of psychological interventions delivered by non-mental health specialists in LMICs in treating mental, neurological and substance use disorders (Van Ginneken *et al.*, 2013) and common mental disorders (Singla *et al.*, 2017) among the adult population.

A growing literature from Pakistan, China, Chile and Mexico suggests that such culturally-adapted task-shared psychosocial interventions can be effective for perinatal depression specifically (Rojas *et al.*, 2007, Rahman *et al.*, 2008, Lara *et al.*, 2010, Gao *et al.*, 2012). This is supported by a recent meta-analysis which reviewed evidence on the effectiveness of psychosocial interventions for perinatal depression in LMICs, specifically when delivered by non-mental health specialists (Clarke *et al.*, 2013). They report that only interventions conducted throughout the perinatal period were effective, but not when interventions took place either in the antenatal or postpartum period. Interestingly, of the 11 studies identified, most focused on health promotion, rather than psychological interventions per se, and included elements such as information and skills development to enhance perinatal health, and opportunities for women to share concerns and receive social support. Both types of interventions were reported to be effective in reducing perinatal depressive symptoms. A similar conclusion was reported by Rahman *et al.* (2013a), who conducted a similar systematic review on the effectiveness of mental health interventions in treating common perinatal mental disorders in LMICs. In their

systematic review, however, they also report that such interventions were beneficial to the children's health, physical growth and development, and interaction with their mother.

Such evidence-based interventions are effective in controlled situations and with homogeneous samples. However, such research methods do not cater for the heterogenous trajectories of depressive symptoms outlined above, and research samples are unlikely to be representative of the populations at risk for perinatal depression in these settings. Also, some have warned against the limitations of randomised controlled trials (RCTs) in assessing the efficiency and feasibility of interventions in real life settings (Tomlinson *et al.*, 2015b). Indeed, it remains unclear how such interventions can be made sustainable in primary care settings, given the extensive training and supervision required, and the high turnover among the already overburdened primary health care staff (Ventevogel, 2014). Also, the use of screening instruments can lead to overdiagnosis or inappropriate referrals to treatment, thus leading to unnecessary use of limited resources and increasing the risk of overburdening an already weak health system (Kagee *et al.*, 2013, Editors, 2015). A review of the progress made since the 2007 call for the scale up of mental health care in LMICs highlights several barriers to scaling up such interventions, including lack of political will, centralisation, lack of trained staff and limited leadership skills among mental health specialists (Eaton *et al.*, 2011). These issues are also relevant to the South African setting.

1.6. Mental health care in South Africa

Despite some improvement in the provision of mental health care in South Africa, the post-Apartheid mental health care system remains underfunded and under-resourced, and still focuses heavily on tertiary psychiatric hospitals (Department of Health, 2013). A situation analysis of the state of mental health care in South Africa conducted in 2008 indicated that only 9.3 staff per 100,000 population were working in mental health, either in the Department of Health or non-governmental organisations (NGOs) (Lund *et al.*, 2008). Currently, the majority of the mental health care focuses on treatment or rehabilitation of severe mental illness, while most of the care for common mental disorders is provided by external agencies such as NGOs (Department of Health, 2013). And yet, Lund *et al.* (2013) reviewed the cost of severe mental disorders as part the SASH national survey and reported that the lost earnings of ZAR29 billion (US$ 2.8 billion) still outweighed the direct spending on mental health.

In line with international recommendations to improve mental health care globally, the integration of mental health care into primary health care was endorsed in the National Mental Health Policy Framework and Strategic Plan (Department of Health, 2013). Its key objective is to provide provinces

with a guide for mental health promotion, prevention of mental illness, treatment and rehabilitation. Among other strategies, the plan emphasises the need to adopt the task-sharing approach to screen for mental disorders (including alcohol and substance use disorders) during pregnancy and the postpartum period, and the need to refer at-risk women for adequate treatment and management. The policy therefore acknowledges the need to include maternal mental health care as part of the antenatal and postnatal care packages, supporting previous research in South Africa (Honikman *et al.*, 2012, Tomlinson *et al.*, 2013).

The Strategic Plan remains poorly implemented, however, and little progress has been made on the provision of mental health care as part of antenatal and postnatal health services, other than through, often time-limited, internationally funded initiatives or local NGOs (Department of Health, 2013). The ward-based outreach teams, recently appointed as part of the primary health care (PHC) Re-engineering Plan adopted in 2010 (Pillay and Barron, 2011), were intended to support the implementation of the Mental Health Strategic Plan. More specifically, the role of community health workers (CHW) which comprise the outreach teams, in addition to other primary health workers, was to contribute to the early detection and referral of women at risk for common mental disorders, as well as provide psychosocial support (Department of Health, 2013). Whilst ongoing, the implementation of the PHC Re-engineering Plan is a slow process (Pillay, 2012). Presently, there are no routine screening, referral or psychological treatment services available for perinatal women in the public sector health care. At best, mental health care provided during pregnancy takes the form of psychoeducation on how to be healthy during pregnancy and on the adverse effects of smoking, alcohol or other substances on the foetus (Sorsdahl *et al.*, 2015). Otherwise, antenatal and postnatal services focus mainly on physical health, including HIV testing and Prevention of Mother To Child Transmission (PMTCT) programmes, and are delivered for free at Midwife Obstetrics Units; these are integrated in primary health care clinics and distributed throughout the country, including more impoverished areas (Rispel and Padarath, 2018).

1.7. Rationale for the thesis

Despite major milestones towards the provision of mental health care and the steps taken to improve primary health care in South Africa, more research is clearly needed to identify the most efficient way to detect, refer and treat women suffering from perinatal depression, particularly in the context of the PHC re-engineering plan and overstretched primary health care staff. Though there is compelling evidence for the risk and burden of perinatal depression in South Africa and other LMICs, little is known about: i) the trajectory of depressive symptoms over the perinatal period, and whether some

women show a natural remission or if women show relatively stable levels of symptoms over time; ii) the risk profiles of women showing different trajectories of perinatal depressive symptoms; iii) the impact of different trajectories, which are characterised by different patterns of severity and chronicity of perinatal depressive symptoms, on child health and development; and iv) the association between depressive symptoms and suicidal risk during the perinatal period and whether this changes over the course of the perinatal period or depending on women's risk profiles and trajectories of depressive symptoms.

Identifying whether there are different trajectories of depressive symptoms over the perinatal period, and whether these are associated with different risk profiles, child outcomes and suicidal risk over time would go a long way in developing efficient methods to identify and manage women who may need more intensive care. Addressing these gaps in the literature would also have important implications on our understanding of the aetiology, course and prognosis of perinatal depression in low-income settings, and would contribute to improving our evaluation of interventions for perinatal depression in controlled research settings. Ultimately, this could contribute to efforts to improve women's and their children's mental and physical health, as well as contribute to breaking the negative cycle of mental health and poverty.

1.8. Aims and objectives

The overall aim of this thesis is to identify the trajectories of perinatal depressive symptoms among low-income women in South Africa, and investigate whether these are associated with psychosocial and economic risk factors, child outcomes and suicidal risk over time. This will be answered by addressing the following four objectives:

1. To systematically review the international literature on latent trajectories of perinatal depressive symptoms and associated risk and symptom profiles;
2. To identify latent trajectories of perinatal depressive symptoms and associated risk factors among low-income women living in Khayelitsha, South Africa, who are at risk for depression antenatally;
3. To identify latent trajectories of perinatal depressive symptoms and associated child development outcomes among low-income women living in Khayelitsha, South Africa;
4. To investigate the association between perinatal depressive symptoms and suicidal behaviours over time among low-income women living in Khayelitsha, South Africa.

Chapters 2 to 5 will address each objective separately, drawing on the results of the previous objectives to inform the methods and analysis presented in the following objective. More specifically, Chapter 2 will report the results of the systematic review, summarising the literature and current knowledge on trajectories of perinatal depressive symptoms globally. Chapters 3 and 4 will address one of the gaps in the literature, that is the lack of evidence on the trajectories of perinatal depressive symptoms in LMICs. In Chapter 3, this will be done among a sample of low-income pregnant women in South Africa who screened positive on the EPDS at their first antenatal visit. This will help identify whether women who would be identified as being at risk for depression antenatally by current advocacy screening efforts show heterogeneous trajectories of depression over the course of the perinatal period. Given that the majority of women are initially at low risk of depression during pregnancy, Chapter 4 will report on the heterogenous trajectories of depressive symptoms among a broader general perinatal population, and extend the results of Chapter 3 by also assessing trajectories in relation to child outcomes. Finally, having identified women who are more likely to suffer from chronic severe depressive symptoms in Chapters 3 and 4, Chapter 5 will assess the risk of suicide in relation to the rate of change in depressive symptoms among women at risk for depression antenatally.

Objectives 3 to 5 will be addressed by conducting secondary data analyses of two RCTs – the Africa Focus on Intervention Research for Mental Health (AFFIRM RCT) (Lund *et al.*, 2014) and the Philani Intervention Programme (Philani RCT) (Rotheram-Borus *et al.*, 2011). The aim of the AFFIRM RCT was to assess the effectiveness of a task-shared six-session psychological intervention for perinatal depression delivered by CHWs. The difference in depressive symptoms between the control and intervention arms was not significant throughout the study, so both arms were combined in Chapters 3 and 5. The aim of the Philani RCT, on the other hand, was to assess the effectiveness of an intervention provided during pregnancy by peer CHWs and focusing on HIV, nutrition, alcohol use and mental health. The intervention did not have an effect on mothers' mental health outcomes. However, differences in child outcomes, breastfeeding and HIV-related behaviours among women at risk for depression between the control and intervention arms were identified. So, for the Philani sample, only the control arm was considered in Chapter 4.

1.8.1. Study settings: Khayelitsha and Mfuleni

Both trials were conducted in Khayelitsha, and participants in the Philani trial were also recruited from a neighbouring smaller settlement called Mfuleni. Khayelitsha and Mfuleni are two of the many township settlements located in the peri-urban region of Cape Town in the Western Cape (Figure 1.2

and 1.3), a province of South Africa marked by extreme inequalities in terms of education, health, income and housing (Statistics South Africa, 2017a).

In isiXhosa, the predominant language spoken in both settlements, Khayelitsha means 'new home'. This is because, in 1983, it was established as a new site to relocate all 'Black' residents from the Cape Peninsula into racially segregated residential areas, part of the marginalisation and alienation meted out by the policies of the Apartheid government. Since the late 1980s, the area has seen an influx of migrants from the rural Eastern Cape in search of work (Ngxiza, 2012). There are now nearly 400,000 residents in Khayelitsha (Table 1.1), which is one of the biggest township settlement in South Africa (Statistics South Africa, 2017a). The majority of residents still have family living in the Eastern Cape, to whom they send remittances and travel to every year.

Table 1.1 Demographic and housing characteristics of Khayelitsha and Mfuleni township settlements (Statistics South Africa, 2011a, b)

	Khayelitsha	Mfuleni
Population size	391,749	52,274
Number of households	118,810	16,804
Average size of household (persons)	3.2	3.0
Education level among adults aged 20 or more (%)		
None	2.6	1.8
Some primary or secondary school	61.6	65.0
Completed secondary school	30.8	29.3
Higher (tertiary) education	4.9	3.9
Housing (%)		
Formal dwellings	44.6	62.5
Flush toilet in dwelling	71.7	86.2
Piped water in dwelling	34.6	52.2
Electricity	80.8	82.9
No household income in past year (%)	18.8	20.5

In the past years, the infrastructure of Khayelitsha has improved somewhat, and additional brick houses have been built. Now 45% of residents live in formal housing, rather than in informal shacks made of tin, plastic, wood and cardboard (Statistics South Africa, 2011a, b). At present, approximately 80% of formal houses and shacks are serviced with electricity, but less than half have access to piped water in the household and the majority of residents instead source their water from communal taps.

Despite new developments, such as new schools, shopping centres and police stations, a central business district now established and fairly acceptable public transport in and around Khayelitsha, the township remains economically marooned from the commercial centre of Cape Town. There are very

few employment opportunities and, according to a 2017 report, 32% of adults in Khayelitsha are unemployed – the highest unemployment rates of the Cape Metro area (Western Cape Government, 2017). The majority of inhabitants of Khayelitsha and Mfuleni still live in extreme poverty, and a fifth of residents in Khayelitsha and Mfuleni report receiving no household income (Statistics South Africa, 2011a, b). According to a study on food insecurity in the Metropolitan district of Cape Town, 68.4% of households in Khayelitsha reported being severely food insecure (Manyise, 2017). The poor quality of life in Khayelitsha and Mfuleni is further exacerbated by the high violence and crime rates, most having doubled or even tripled in the past ten years (Statistics South Africa, 2018b). In 2018, approximately 900 assaults and murders were reported in both Khayelitsha and Mfuleni, individually (Statistics South Africa, 2018a).

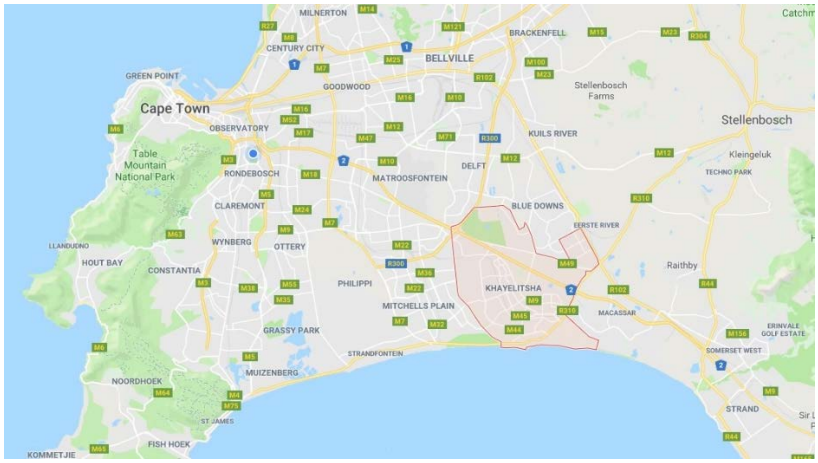

Figure 1.2 Geographical location of Khayelitsha

The poor housing infrastructure and dense population are also conducive to poor health, and the burden of HIV and TB in Khayelitsha is one of the highest in South Africa: it is estimated that 1400 per 100,000 people suffer from tuberculosis annually (Medecins Sans Frontieres, 2011), and 34% of pregnant women are HIV positive (National Department of Health, 2014). The introduction of antiretroviral and PMTCT programmes, available at all provincial and municipal clinics located throughout the township, has helped reduce the infant mortality rate to 32 per 1000 births (Groenewald *et al.*, 2008).

Overall, Khayelitsha and Mfuleni are representative of many other township settlements in the Western Cape and South Africa. Indeed, across all settlements' enumeration areas in the country, approximately 7% of adults report no schooling and 5% report no household income. About one fifth live in informal dwellings and only 38%, 22% and 42% of residents have access to piped drinking water, flush toilet and electricity, respectively (Housing Development Agency, 2012).

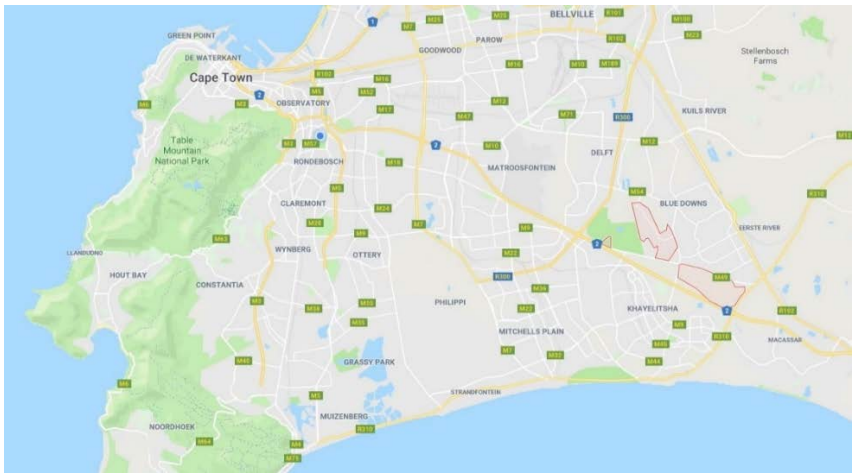

Figure 1.3 Geographical location of Mfuleni

1.9. Contribution to the AFFIRM and Philani RCTs

I was involved in the formative phase of the AFFIRM trial, as well as in the trial data collection, data analysis and interpretation. More specifically, I contributed to the development of the counselling intervention for perinatal depression and provided strategic support in the recruitment and follow-up of participants. I also developed the statistical analysis plan in collaboration with the trial statistician. Once the data were unblinded to collaborators, I was in charge of cleaning the data, formatting it for public use and running the trial primary and secondary analyses. The manuscript on the main trial findings is currently under review (Lund *et al.*, Under review). My contribution to the Philani trial, however, was more limited, and concentrated mostly on cleaning and adapting the dataset for use for this thesis. Permission to access the dataset for the purpose of this thesis was granted by the two principal investigators, Mark Tomlinson and Mary Jane Rotheram-Borus.

Chapter 2. Systematic review on trajectories of perinatal depressive symptoms

2.1. Brief overview

The aim of the study in this Chapter was to review the growth curve mixture modelling (GCMM) literature investigating trajectories of perinatal maternal depressive symptoms and associated risk factors. A systematic search of peer-reviewed articles published until November 2015 was conducted in seven databases. Articles using GCMM to identify trajectories of perinatal depressive symptoms were considered. Symptoms had to be assessed at least three times, any time from pregnancy to two years postpartum (PROSPERO; 2016:CRD42016032600). Eleven studies met inclusion criteria. All reported a low-risk trajectory, characterised by stable low depressive symptoms throughout the perinatal period. A stable moderate-high or high symptom trajectory was reported in eight of 11 studies, suggesting a high-risk group with persistent depressive symptoms. Six studies also reported transient trajectories, with either increasing, decreasing or episodic depressive symptoms. None of the demographic, personality or clinical characteristics investigated systematically differentiated groups of women with different symptom trajectories, within or across studies. Thus, it is difficult to differentiate women at high or low risk for specific perinatal depression trajectories. Limitations include the fact that a meta-analysis was not possible, and that the studies' settings and inclusion criteria limit the generalisability of the findings to low-risk, middle- to high-income women. In conclusion, relatively similar trajectories of perinatal depressive symptoms were identified across studies. Evidence on factors differentiating women assigned to different trajectories was inconsistent. Research with larger samples and in more diverse settings is needed to inform services and policies on how and when to effectively identify subgroups of women at high risk for perinatal depression.

2.2. Introduction

The high prevalence of perinatal maternal depression is a well-documented global phenomenon. In high-income countries, common mental disorders are reported on average by 10% and 13% of pregnant and postnatal women, respectively (O'hara and Swain, 1996). A recent review of the literature suggests that in low- and middle-income countries (LMICs), approximately 16% of women experience antenatal depression and 20% postnatal depression (Fisher *et al.*, 2012). Perinatal

depression contributes to the global burden of disease, both directly, given that depression accounts for over 40% of disability adjusted life years caused by mental disorders (Whiteford *et al.*, 2013), and indirectly, through associations with suicidal behaviour (World Health Organization, 2008a, Rahman *et al.*, 2013b). Untreated perinatal depression also has detrimental effects on birth outcomes (Lusskin *et al.*, 2007b), as well as on children's health and socio-emotional development (Hayes and Sharif, 2009, Wachs *et al.*, 2009).

Effective prevention of perinatal depression and associated poor maternal and child health outcomes requires understanding when women are most at risk and what factors are associated with the disorder's onset, severity and chronicity. To achieve this aim, longitudinal mixed-effects and latent growth curve models are commonly used to assess the progression of depressive symptoms during the perinatal period. Though these methods allow for individual variability, they assess the average pattern of change in symptoms over time and assume individuals belong to the same underlying population, represented by a single growth curve. Yet, existing evidence suggests heterogeneity in time of onset and progression of perinatal depressive symptoms. While some studies have identified antenatal depression as a major risk factor for postpartum depression (Robertson *et al.*, 2004), others have shown a natural decline in depressive symptoms during pregnancy and the postpartum period, or symptoms developing only after giving birth (Stowe and Nemeroff, 1995, Gavin *et al.*, 2005). These methods' assumptions therefore risk oversimplifying the complex process involved in the development and progression of perinatal depression.

An emerging, alternative method which addresses this limitation is a person-centred, latent class approach, which allows researchers to identify and describe underlying subgroups or classes within a population, based on different patterns of symptom change, or trajectories (Ram and Grimm, 2009, Leiby, 2012). Within this exploratory approach, latent growth curve models, often referred to as growth curve mixture models (GCMM) (Leiby, 2012), are a flexible subtype of models that do not require the researcher to predefine the number of trajectories being identified. This is an advantage, particularly given that predefining the number of trajectories is likely to increase the likelihood of poor model fit (Ram and Grimm, 2009).

When GCMM is used, several models are generated. In each model, parameters of growth trajectories and inter-individual variation are estimated for each latent class or trajectory. The intercept is the initial level of symptom, and the slope is the rate in change of symptom level over time. In addition, posterior probability estimates in each model indicate the probability that an individual belongs to each trajectory. The optimal model of trajectories is selected using a range of fit statistics, including

model fit indices, estimated posterior probabilities, and likelihood ratio tests. Post-hoc tests, such as multinomial regressions, are often performed to compare baseline characteristics or specific outcomes of individuals classified into the different trajectories. These analyses can also help assess whether the latent trajectories identified make pragmatic sense.

GCMM has been used in the analysis of mental health-related outcomes, including binge drinking (Tucker *et al.*, 2003), psychosocial wellbeing (Zammit *et al.*, 2012), and anxiety and mood disorders (Nandi *et al.*, 2009). It has also increasingly been used to explore trajectories of depressive symptoms among women during the perinatal period (Mora *et al.*, 2009, Sutter-Dallay *et al.*, 2012b, Kuo *et al.*, 2014). To our knowledge, the findings of these studies have not yet been systematically synthesised. An overview of these studies would help identify how and when trajectories of perinatal depressive symptoms differ, and whether this is consistent across populations. Findings could also have implications for identifying optimal timing of screening for perinatal depression and for the content or focus of screening required to differentiate women with chronic symptoms from those with transient levels. Therefore, the aim of this study was to systematically review the growth curve mixture modelling literature investigating the trajectories and associated risk factors for maternal depressive symptoms during the perinatal period.

2.3. Methods

The review protocol was registered with PROSPERO (2016:CRD42016032600) and was developed and reported according to the MOOSE guidelines (Stroup *et al.*, 2000).

2.3.1. Search strategy

A systematic search of peer-reviewed articles was conducted in the following seven databases: MEDLINE, Embase (via Scopus), the Cochrane Library (Cochrane Database of Systematic Reviews), Web of Science, PsychINFO, CINAHL and Africa Wide. A range of keywords and database subject headings were used to capture four key concepts combined using the Boolean term 'AND': (1) depressive symptoms during the perinatal period, (2) perinatal depressive symptoms trajectories, (3) factors associated with symptom trajectories, and (4) longitudinal designs using latent variable modelling approaches (see Table 2.1).

There were no publication date or language restrictions. Articles considered for review were those which reported the use of GCMM to identify trajectories of perinatal depressive symptoms and

associated risk factors. These could be based on primary data from cohort studies or based on secondary data from randomised controlled trials (RCTs), if no statistical differences in depressive symptoms were reported between the control and intervention arms. If a study reported only on trajectories and outcomes, rather than risk factors, results related to trajectories were still included in this review.

Table 2.1 Database search strategy for the systematic review

Concept	Search terms
1. perinatal depressive symptoms	(depression OR depressive symptoms OR mood OR dysthymia OR distress OR mental health) AND (perinatal OR antenatal OR prenatal OR pregnancy OR pregnant OR birth OR postnatal OR postpartum OR maternal)
2. trajectories	trajectory OR trajectories OR evolution OR evolutionary OR progress OR progression OR development OR growth OR prognosis OR remission OR epidemiology OR persistence OR chronic OR change
3. factors associated with trajectories	profiles OR "risk factors" OR symptoms OR "socio-economic" OR socioeconomic OR "psychosocial factors" OR correlates OR "prognostic factors" OR predictors
4. longitudinal design using latent variable modelling	cohort OR prospective OR longitudinal OR modelling OR modeling OR follow-up OR latent classes OR "growth mixture modelling"

Depressive symptoms were defined as any sub-clinical (distress) or clinical depressive symptomatology, assessed on a longitudinal scale, either using a validated screening tool or a diagnostic assessment based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Statistical Classification of Diseases and Related Health Problems (ICD) criteria. However, studies were excluded if depressive symptoms were investigated in the context of a comorbid primary mental disorder (e.g. anxiety, bipolar, schizophrenia, psychosis). This criterion was put in place to exclude studies investigating perinatal women without a primary presentation of depression. Psychological morbidities would likely influence the severity and course of depressive symptoms, and it would be difficult to distinguish actual change in depressive symptoms over time from change in depressive symptom as a function of the comorbid primary diagnosis. Trajectories were conceptualised as the change in depressive symptoms during the perinatal period, defined as pregnancy and up to two years after birth. Assessments could be conducted during pregnancy, during the postpartum period, or during pregnancy and the postpartum period. A minimum of four assessment points has been recommended when performing GCMM, as fewer assessments limit the functions that can be modelled, and therefore the type and number of trajectories that can be generated (Johnson *et al.*, 2007, Berlin *et al.*, 2014). Given the limited number of studies generated in a pilot search with this criterion, the authors decided to include studies with a minimum of three

depression symptom assessments. In cases where additional assessments were conducted outside of the two-year postpartum period, the study was excluded as this would shape the overall estimates of symptom trajectory. Risk factors were defined as any clinical, socio-demographic or socio-economic factors measured during the first two assessments.

Abstracts generated from the search were recorded and transferred to Endnote, where duplicates were identified and deleted. After irrelevant titles were excluded by one reviewer (ECB), two pairs of two independent reviewers (ECB and JB, or ECB and SM) screened the remaining abstracts and full texts. Articles selected by both reviewers were automatically included in the next review step. When reviewers did not agree, a third reviewer (JB or SM) made a final decision. The number of articles selected at each step of the review process were captured, as well as the main reason for exclusion (Figure 2.1). A single reviewer (ECB) extracted the following data from each full-text article: study setting, participant characteristics, the number and timing of assessments, instruments used to measure depressive symptoms, statistical analyses performed, and covariates included in the analyses. The number and nature of trajectories identified, as well as any risk factors associated with these trajectories, were also recorded. Identification of studies' biases and limitations were based on the Newcastle-Ottawa quality assessment scale for cohort studies (Wells *et al.*, 2012). This section covered information related to the size and representativeness of the sample, the number of assessment points, attrition rate and statistical methods used to deal with missing data, as well as the number and nature of considerations taken to select the optimal model from the GCMM. Based on these criteria, a score out of 12 was generated to rate the quality of each study; each study was then classified as either poor (+), average (++) or good (+++).

The search was conducted in November 2015, the screening and review processes were finalised in January 2016, and data extraction was completed in February 2016.

2.3.2. Data analysis

Given the lack of model parameters (i.e. slopes, intercepts, and variances of the latent trajectories) reported in the identified studies, a meta-analysis could not be conducted. Instead, a qualitative synthesis of findings is presented, highlighting the most common trajectories and risk factors reported across the studies identified. To help visualise and compare the different trajectories identified across the studies in the review, and because different instruments were used to measure depressive symptoms, the average depression score at each time point for each trajectory was standardised in relation to the severity cut-off of the scale indicated by authors. Standardization was completed by

transforming the difference between the average depressive score at each time of assessment and the severity cut-off score of the scale indicated by the authors into a percentage of the overall score of the scale used. A positive percentage therefore indicated a score above the cut-off and a negative percentage indicated a score below the cut-off. When a severity cut-off was not indicated by authors, the recommended cut-off for the instrument was used.

2.4. Results

2.4.1. Study selection

The search terms identified 5388 articles, of which 789 abstracts were screened for eligibility (Figure 2.1). In total, 55 articles were selected for full-text review; 19 of these did not clearly state the method of analysis used in the reviewed abstract. The majority of articles (95%) were written in English. The three non-English full-text articles (two in Korean and one in Japanese) were excluded after a translation of the analysis section revealed that a growth curve modelling approach was not used. One article did not strictly fit the two-year postpartum period criterion (Mora *et al.*, 2009), with a final assessment conducted at 25 months postpartum. As this criterion was used to exclude articles with assessments occurring later in childhood or during adolescence, and given the article's relevance to the topic of the review, the authors opted to include this article.

Eleven articles were identified for final review (Table 2.2). All studies reported in these articles were conducted in high-income countries: two in Taiwan (Kuo *et al.*, 2012, Kuo *et al.*, 2014), one in France (Sutter-Dallay *et al.*, 2012b), one in Finland (Vänskä *et al.*, 2011), and the remaining seven in the United States (Mora *et al.*, 2009, Ramos-Marcuse *et al.*, 2010, Christensen *et al.*, 2011, Marcus *et al.*, 2011, Glasheen *et al.*, 2013, Lee *et al.*, 2014, Parade *et al.*, 2014). All studies were published between 2009 and 2014. Ten of the 11 studies investigated perinatal depressive symptoms among adult women; the remaining study was with adolescent women in the postpartum period (Ramos-Marcuse *et al.*, 2010). The majority of studies (n = 6) investigated risk factors only in relation to trajectories, three studies investigated risk factors and outcomes simultaneously (Christensen *et al.*, 2011, Vänskä *et al.*, 2011, Glasheen *et al.*, 2013), and two studies investigated outcomes associated with trajectories (Ramos-Marcuse *et al.*, 2010, Marcus *et al.*, 2011).

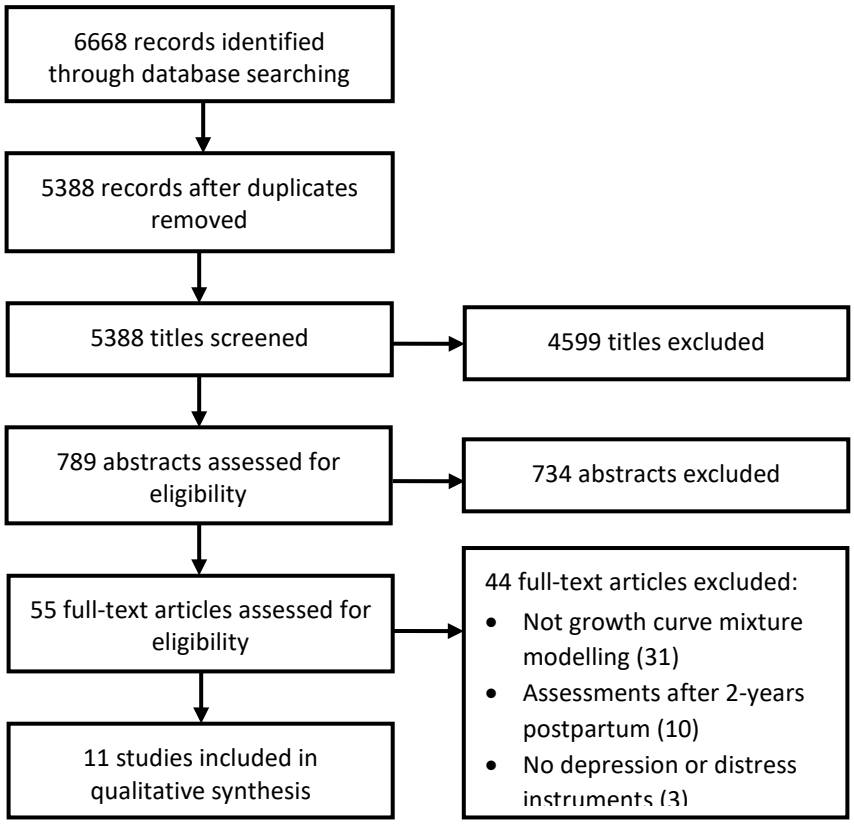

Figure 2.1 Search process for studies investigating trajectories of perinatal depression using growth curve mixture modelling

2.4.2. Study characteristics and quality

Tables 2.2 and 2.3 provide an overview of the recruitment, inclusion and exclusion criteria, assessments and statistical methods employed across the different studies identified in this review. The study's quality ratings are also reported in Table 2.3. Three studies were considered of good quality (score 8-12) (Mora *et al.*, 2009, Glasheen *et al.*, 2013, Kuo *et al.*, 2014), five as average (score 5-7) (Ramos-Marcuse *et al.*, 2010, Vänskä *et al.*, 2011, Kuo *et al.*, 2012, Sutter-Dallay *et al.*, 2012b, Lee *et al.*, 2014), and three as relatively poor (score 1-4) (Christensen *et al.*, 2011, Marcus *et al.*, 2011, Parade *et al.*, 2014). The main reason for the low score for the Marcus et al (2011) study was poor statistical methods or reporting, whereas poor design (such as sample size and attrition) was the main reason for the low scores in the Parade et al. (2014) and Christensen et al. (2011) studies.

Sample sizes varied widely across studies (range: n = 98 (Parade *et al.*, 2014) to n = 1735 (Mora *et al.*, 2009)), with the majority reporting samples between 120 and 600. A small sample was acknowledged as a limitation by the authors in several of the studies (Sutter-Dallay *et al.*, 2012b, Kuo *et al.*, 2014,

Parade *et al.*, 2014). Five of the 11 studies reported analyses on secondary data (Mora *et al.*, 2009, Ramos-Marcuse *et al.*, 2010, Christensen *et al.*, 2011, Sutter-Dallay *et al.*, 2012b, Lee *et al.*, 2014). Of these five studies, three utilised data from RCTs. These assessed an intervention for perinatal depression among Hispanic women who reported sub-clinical depressive symptomatology but did not have a diagnosis of major depression (Christensen *et al.*, 2011); a weight loss program among overweight or obese women (Lee *et al.*, 2014); and a parenting and adolescent development promotion program for low-income families qualifying for government grants (Ramos-Marcuse *et al.*, 2010). Two of these studies reported that depressive symptoms were not significantly different between the control and intervention arms at any assessment point (Christensen *et al.*, 2011) (Ramos-Marcuse *et al.*, 2010), and one reported that there were no differences in intercept, slope or curvature between the two arms in the overall symptom trajectory generated through latent growth modelling (Lee *et al.*, 2014). This meant that the intervention did not significantly differentiate the two arms and thus should not have biased the trajectories of depressive symptoms generated by the GCMM.

The majority of studies included in this review excluded women if they reported severe mental health or substance abuse problems (Christensen *et al.*, 2011, Marcus *et al.*, 2011, Sutter-Dallay *et al.*, 2012b), chronic illnesses (Ramos-Marcuse *et al.*, 2010, Kuo *et al.*, 2012, Kuo *et al.*, 2014), and usually included women who had a singleton and/or an uncomplicated pregnancy (Vänskä *et al.*, 2011, Kuo *et al.*, 2012, Sutter-Dallay *et al.*, 2012b, Kuo *et al.*, 2014). The limited representativeness of the samples was acknowledged by most authors (Ramos-Marcuse *et al.*, 2010, Christensen *et al.*, 2011, Vänskä *et al.*, 2011, Kuo *et al.*, 2012, Sutter-Dallay *et al.*, 2012b, Kuo *et al.*, 2014). Both Christensen et al. (2011) and Marcus et al. (2011) investigated depressive symptoms among women at high risk for depression but without a diagnosis. Three studies were more inclusive, and only restricted the criteria to age (usually above 18 years old) and language (speaking local language) (Mora *et al.*, 2009, Glasheen *et al.*, 2013, Parade *et al.*, 2014). However, the inclusion criteria were unclear in Parade *et al.* (2014)'s study, and the data used in the Glasheen et al.'s study (2013) dated from 1982 and 1985 and may be less representative now.

Table 2.2 Design, recruitment and data collection methods of the 11 studies included in the systematic review

Study	Location	Sample size	Population	Inclusion/exclusion criteria	Time of recruitment	Outcome of interest	Assessments
Christensen et al (2011)	Washington DC, US (urban)	215	Pregnant women undergoing preventive intervention for perinatal depression; Mean age 25.4	*Inclusion criteria*: 18 to 35 years; Hispanic; less than 25 weeks pregnant; CES-D-20 score >15 but not currently depressed. *Exclusion criteria*: report smoking, drinking alcohol or using illicit drugs, or meet criteria for other major mental disorder or significant psychosocial problems	Antenatal (average 18 weeks gestation)	BDI-II: cut-off of 16 suggesting depressive symptomatology	5 assessments: First assessment:18 weeks gestation; Last assessment: 12 months postpartum
Glasheen et al (2013)	Michigan, US (urban)	577	General perinatal population; Mean age 22.9	*Inclusion criteria*: at least 3 of 5 assessments; mother-child pair available at 16-year follow-up *No other exclusion criteria*	Antenatal, first trimester	CES-D-20 (no cut-off indicated)	5 assessments First assessment: first trimester of pregnancy; Last assessment: 18 months postpartum
Kuo et al (2012)	Central Taiwan	121	General perinatal population; Mean age 33.4	*Inclusion criteria*: 20 years or older; singleton pregnancy *Exclusion criteria*: perinatal complications, chronic medical history	Antenatal, third trimester	EPDS: cut-off of 10 suggesting high level of symptoms	4 assessments First assessment: third trimester; Last assessment: 7 days postpartum
Kuo et al (2014)	Central Taiwan	139	General perinatal population; Mean age 31.2	*Inclusion criteria*: 20 years or older; considered for caesarean section, *Exclusion criteria*: other perinatal complications; chronic medical illness	Antenatal, third trimester (average 37 weeks gestation)	EPDS: cut-off of 13 suggesting probable case of depression	5 assessments First assessment: third trimester; Last assessment: 6 months postpartum
Lee et al (2014)	North Carolina, US	844 (from two RCTs, AMP and KAN-DO)	Overweight or obese perinatal population Mean age 31.7	*Inclusion criteria*: BMI>25 before pregnancy; 18 years or older; English-speaking AMP: able to walk a mile KAN-DO: maximum 6 months postpartum at recruitment; pre-schooler in the home; no medical complications	Postnatal; AMP: 2 months postpartum KAN-DO: 6 months postpartum	EPDS: cut-off of 13 suggesting postpartum depression	3 assessments per RCT (one assessment in common), 5 altogether First assessment: 1-7 months postpartum; Last assessment: 24 months postpartum
Marcus et al (2011)	Michigan, US	154	General perinatal population; 48% between 20-30 years 50% between 31-40 years	*Inclusion criteria*: 21 years or older, EPDS score >10 but not currently depressed; fluent in English *Exclusion criteria*: adoption plan; chronic medical condition or use of medication that impact LHPA; treated with psychotropic medication; substance abuse; eating disorder; bipolar illness	Antenatal, between 8- and 28-weeks gestation	BDI: cut-off of 20 criteria for further assessment with SCID (no cut-off indicated for severity)	3 assessments First assessment: 28 weeks; Last assessment: 37 weeks

Study	Location	Sample size	Population	Inclusion/exclusion criteria	Time of recruitment	Outcome of interest	Assessments
Mora et al (2009)	Philadelphia, US (urban)	1735	General perinatal population; Mean age 23.9	*Inclusion criteria*: English- or Spanish-speaking; singleton intrauterine pregnancy; at least one postpartum interview; live birth *No other exclusion criteria*	Antenatal, first antenatal care visit (average 15 weeks gestation)	CES-D-20: cut-off of 16 indicating significant levels of symptoms	4 assessments First assessment: at first antenatal visit (15 weeks gestation); Last assessment: 25 months postpartum
Parade et al (2014)	North-East US (state not specified)	98	General perinatal population; Mean age 29.0	*Inclusion criteria*: primiparous, 20 years or older *No other exclusion criteria*	Antenatal, 8 weeks before expected date of delivery (EDD)	CES-D-20 (15 items - excluding 5 items relating to somatic symptoms) Not cut-off indicated	4 assessments First assessment: 8 weeks prior to EDD; Last assessment: 24 weeks postpartum
Ramos-Marcuse et al (2010)	Baltimore, Maryland, US (urban)	181	Low-income general perinatal population; Mean age 16.3	*Inclusion criteria*: 17 years or younger, first time delivery, African American, low-income (eligible for WIC, family income under 185% of poverty level); living with their mother *Exclusion criteria*: chronic physical illnesses	Postnatal, shortly after delivery	BDI: cut-off of 9 suggesting risk for depression	3 assessments First assessment: within 3 weeks of delivery; Last assessment: 24 months postpartum
Sutter-Dallay et al (2012)	Bordeaux, France (urban)	579	General perinatal population; Mean age 29.4	*Inclusion criteria*: French-speaking, living in catchment area of hospital, less than one week of hospitalisation for pregnancy complications *Exclusion criteria*: planned or unplanned CS delivery; personal history of chronic severe mental illness; multiple pregnancy or in vitro fertilisation for current pregnancy; premature birth	Antenatal, third trimester	CES-D-20: cut-off of 16 indicating clinically significant level of depressive symptoms	8 assessments First assessment: 8 months gestation; Last assessment: 24 months postpartum
Vänskä et al (2011)	Finland (city not specified)	805	Pregnant women who have undergone successful infertility treatment; Mean age 33.1	*Inclusion criteria*: Finnish-speaking Intervention group: successful singleton pregnancy after infertility treatment Control group: no infertility history *No other exclusion criteria*	Antenatal, 18-20 weeks gestation	GHQ-36: cut-off of 9 clinical criterion for psychiatric disorder; BDI-13: cut-off of 5 suggesting mild depression (after recoding items)	3 assessments First assessment: 18-20 weeks gestation; Last assessment: 12 months postpartum

AMP: Active Mothers Postpartum; BDI: Beck Depression Inventory; BMI: Body mass index; CES-D-20: Centre for Epidemiological Studies – Depression scale; EDD: expected date of delivery; EPDS: Edinburgh Postnatal Depression Scale; GHQ-36: General Health Questionnaire – 36 items; KAN-DO: Kids and Adults Now! – Defeat Obesity; LHPA: limbic hypothalamic pituitary axis; WIC: Women, Infants and Children (financial assistance for pregnant, postpartum and breastfeeding women); US: United States of America.

Seven studies conducted more than the required three assessments of depression for inclusion in the review (range: four (Mora *et al.*, 2009, Kuo *et al.*, 2012, Parade *et al.*, 2014) to eight (Sutter-Dallay *et al.*, 2012b)). The length of the trajectories modelled varied extensively. The longest trajectories were reported by Mora *et al.* (2009), where women were followed from their first trimester through two years postpartum. The shortest study period investigated was 9 weeks in Marcus *et al.* (2011)'s study and was the only study to be conducted solely during pregnancy. Two studies focused on postpartum depressive symptoms only (Ramos-Marcuse *et al.*, 2010, Lee *et al.*, 2014), while the remaining eight studies investigated depressive symptoms both during pregnancy and the postpartum period (Mora *et al.*, 2009, Christensen *et al.*, 2011, Vänskä *et al.*, 2011, Kuo *et al.*, 2012, Sutter-Dallay *et al.*, 2012b, Glasheen *et al.*, 2013, Kuo *et al.*, 2014, Parade *et al.*, 2014).

All studies used validated depressive screening tools to assess depressive symptoms. Tools used included versions of the Centre for Epidemiological Scale – Depression (CES-D-20; (Radloff, 1977); n = 4), the Beck Depression Inventory (BDI; (Beck *et al.*, 1961), n = 4)), or the Edinburgh Postnatal Depression Scale (EPDS; (Cox *et al.*, 1987), n = 3).

GCMM was conducted in Mplus (Muthén and Muthén, 1998-2015) or SAS (Jones *et al.*, 2001, SAS Institute Inc, 2006). The majority of studies reported conducting growth mixture modelling (Mora *et al.*, 2009, Christensen *et al.*, 2011, Marcus *et al.*, 2011, Vänskä *et al.*, 2011, Kuo *et al.*, 2012, Glasheen *et al.*, 2013), which allows for individual variability within each trajectory. Other studies used latent class growth modelling (Lee *et al.*, 2014), group-based trajectory modelling (Kuo *et al.*, 2014), semi parametric mixture models (Ramos-Marcuse *et al.*, 2010, Sutter-Dallay *et al.*, 2012b) or unconditional latent class growth analysis (Parade *et al.*, 2014). Nearly all studies reported using a combination of information criteria fit indices and estimated posterior probabilities to identify the optimal model (Mora *et al.*, 2009, Ramos-Marcuse *et al.*, 2010, Christensen *et al.*, 2011, Vänskä *et al.*, 2011, Sutter-Dallay *et al.*, 2012b, Glasheen *et al.*, 2013, Kuo *et al.*, 2014, Lee *et al.*, 2014). Likelihood ratio tests were also utilised in some of the studies (Mora *et al.*, 2009, Christensen *et al.*, 2011, Glasheen *et al.*, 2013, Parade *et al.*, 2014). Two studies reported using the Bayesian information criterion (BIC) only (Marcus *et al.*, 2011, Kuo *et al.*, 2012). However, all studies also applied some level of theoretical interpretability to identifying the optimal model, especially when fit statistics indicated that multiple models fit equally well.

Attrition rates, which were reported for eight of 11 studies, are indicated in Table 2.4 (Mora *et al.*, 2009, Ramos-Marcuse *et al.*, 2010, Marcus *et al.*, 2011, Vänskä *et al.*, 2011, Kuo *et al.*, 2012, Glasheen *et al.*, 2013, Kuo *et al.*, 2014, Lee *et al.*, 2014). The other three studies provided no information on the

average number of assessments conducted per participant, or the number of participants assessed at each time point (Christensen *et al.*, 2011, Sutter-Dallay *et al.*, 2012b, Parade *et al.*, 2014). Attrition or average number of assessments per participant were reported differently across the studies: four studies reported that at least 70% of the sample received all assessments (Ramos-Marcuse *et al.*, 2010, Kuo *et al.*, 2012, Glasheen *et al.*, 2013, Kuo *et al.*, 2014), one study reported completion of all assessments by 66% of the sample (Vänskä *et al.*, 2011), and one reported that only half completed all assessments (Mora *et al.*, 2009). Marcus *et al.* (2011) did not provide information on the proportion of the sample completing all assessments, but did indicate that 91% of the sample completed at least two out of three assessments. Similarly, Lee *et al.* (2014) reported an average of 2.5 and 1.9 assessments completed by participants in the two RCTs used in their analyses. The authors of this study did acknowledge attrition as a limitation but argued that the expectation maximisation algorithm employed though Mplus dealt with missing data limited attrition bias.

Out of the eight studies reporting attrition, two did not provide any information on how attrition was dealt with (Ramos-Marcuse *et al.*, 2010, Glasheen *et al.*, 2013). One study imputed multiple missing depression measures using PROC MI in SAS (Marcus *et al.*, 2011). The others used full-information maximum likelihood estimation methods that are robust to data missing at random, either in SAS (Kuo *et al.*, 2012, Kuo *et al.*, 2014) or Mplus (Mora *et al.*, 2009, Vänskä *et al.*, 2011, Lee *et al.*, 2014). These estimations allow all available depression score data of an individual to be used in estimation and thus is an optimal estimator for GCMM (Little *et al.*, 2014).

2.4.3. Number and shape of trajectories

The number and shape of trajectories reported in each study are summarised in Table 2.4. The figures illustrating standardised depression scores over time for all trajectories for each study are also presented in Figures 2.2 and 2.3. The horizontal full line in the figures indicates the severity cut-off, while the vertical full line marks the time of birth. Where studies report secondary data as part of an RCT (Ramos-Marcuse *et al.*, 2010, Christensen *et al.*, 2011, Lee *et al.*, 2014), the timing of the intervention in relation to the assessments is indicated with a horizontal arrow. In the case of very short trajectories (Marcus *et al.*, 2011, Kuo *et al.*, 2012, Kuo *et al.*, 2014), the time axis was adjusted (Figure 2.3). For all other studies, the time scale ranged from the start of pregnancy to 25 months postpartum (34 months after the start of pregnancy) (Figure 2.2).

Table 2.3 Statistical methods of the 11 studies included in the systematic review

Study	Data used	Intervention	Aim of analysis	Analytical approach	Variables controlled for	Method used for missing data	Considerations in model selection	Study quality
Christensen et al (2011)	Secondary (RCT)	Preventive intervention for perinatal depression	Trajectories, risk profiles and outcomes	Trajectories: growth mixture modelling (Mplus); Risk factors: multinomial logistic regression	Demographic, psychosocial characteristics and randomization status for adjusted logistic regression models	Not specified	Information criteria fit indices: BIC and ABIC Estimated posterior probabilities: entropy, sample size of latent trajectories Likelihood ratio tests: BLRT	+
Glasheen et al (2013)	Secondary	None	Trajectories, risk profiles and outcomes	Trajectories: growth mixture modelling (Mplus); Risk factors: logistic and multinomial regression analyses	Demographic characteristics, social support, pregnancy, labour and delivery complications, substance use for regression models	Not specified	Information criteria fit indices: BIC, AIC, Estimated posterior probabilities: entropy Likelihood ratio tests: LMR*	+++
Kuo et al (2012)	Primary	None	Trajectories and risk profiles	Trajectories: growth mixture modelling (SAS); Risk factors: multinomial logistic regression	Parity, education, prenatal employment, prenatal exercise, mode of birth, sleep quality for regression models	PROC TRAJ (SAS): maximum likelihood estimation	Information criteria fit indices: BIC	++
Kuo et al (2014)	Primary	None	Trajectories and risk profiles	Trajectories: group-based trajectory modelling (SAS); Risk factors: logistic regressions	Age, parity, education, pregnancy BMI, use of patient-controlled analgesics (PCAs) and sleep quality for regression models	PROC TRAJ (SAS): maximum likelihood estimation	Information criteria fit indices: BIC Sample size of latent trajectories	+++
Lee et al (2014)	Secondary (RCT)	Weight loss (diet and exercise)	Trajectories and risk profiles	Trajectories: latent growth modelling and latent class growth analysis (Mplus); Risk factors: multinomial logistic regression	Maternal BMI, parity, study (KAN-DO vs. AMP) and arm (control vs. intervention) for LCGA and regression models	Full information maximum likelihood OR expectation maximisation algorithm	Information criteria fit indices: BIC Estimated posterior probabilities: entropy Sample size of latent trajectories	++
Marcus et al (2011)	Primary	None	Trajectories and outcomes	Trajectories: mixture growth curve approach (SAS)	n/a	Imputed missing values using Proc MI (SAS)	Information criteria fit indices: BIC	+

Study	Data used	Intervention	Aim of analysis	Analytical approach	Variables controlled for	Method used for missing data	Considerations in model selection	Study quality
Mora et al (2009)	Secondary (Cohort)	None	Trajectories and risk profiles	Trajectories: growth mixture modelling (MPlus); Risk factors: bivariate analyses (chi square and analysis of variance), multinomial regression	Adjusting for all covariates (maternal characteristics) in regression models	Expectation-maximization algorithm	Estimated posterior probabilities: entropy Information criteria fit indices: BIC, AIC, ABIC Likelihood ratio tests: BLRT Sample size of latent trajectories	+++
Parade et al (2014)	Primary	None	Trajectories and risk profiles	Trajectories: unconditional latent class growth analysis (using Mplus); Risk factors: analyses not specified	Education in latent class growth analysis; education, family income, romantic relationship length and type in regression models	Not specified	Information criteria fit indices: BIC Likelihood ratio tests: BLRT	+
Ramos-Marcuse et al (2010)	Secondary (RCT)	Promoting parenting and adolescent development	Trajectories and outcomes	Trajectories: group-based modelling (semiparametric - using PROC TRAJ, in SAS); Risk factors: polynomial function, analysis of variance and pairwise comparisons	RCT arm not controlled for (no difference in depressive symptoms); arm allocation in post-hoc analyses	Not specified	Information criteria fit indices: BIC Sample size of latent trajectories	++
Sutter-Dallay et al (2012)	Secondary (Cohort)	None	Trajectories and risk profiles	Trajectories: semiparametric mixture models using PROC TRAJ (SAS); Risk factors: multinomial logistic regression	Adjusting for all covariates in the regression model; education excluded from regression due to collinearity	Not specified	Information criteria fit indices: BIC Average posterior probability Sample size of latent trajectories	++
Vänskä et al (2011)	Primary	None	Trajectories, risk profiles and outcomes	Trajectories: mixture modelling (Mplus); Risk factors: ANCOVA	Current psychological distress (based on GHQ36) and parity at recruitment in ANCOVA	Missing-data method (Mplus)	Information criteria fit indices: BIC, AIC, ABIC, Likelihood ratio tests: VLMR, LMR and BLRT Individual and average posterior probabilities	++

ABIC sample size adjusted Bayesian information criterion; AIC: Akaike information criterion; BIC: Bayesian information criterion; BLRT: bootstrap likelihood ratio test; CBT: cognitive behavioural therapy; LMR: Lo-Mendell-Rubin adjusted likelihood ratio test; RCT: randomised controlled trial; VLMR: Vuong-Lo-Mendell-Rubin likelihood ratio test.

The severity cut-off on the instrument measuring depressive symptoms was not indicated in three studies (Marcus *et al.*, 2011, Glasheen *et al.*, 2013, Parade *et al.*, 2014). For this reason, a cut-off of 16 was used for the CES-D-20 in Glasheen et al. (2013), as recommended by Weissman *et al.* (1977). In Parade et al. (2014), where five items were dropped from the original CES-D-20 scale, the cut-off was readjusted from 16 to 12. Finally, the recommended cut-off of 16 for the BDI during pregnancy (Holcomb Jr *et al.*, 1996) was used for standardizing the Marcus *et al.* (2011) findings. For comparison purposes, this cut-off was also used to calculate standardised BDI scores in Ramos-Marcuse et al (2010)'s study, instead of the cut-off of 9 suggested and used by the authors.

The number of trajectories identified and reported ranged from two to five, with the most common number of trajectories being 3 (Ramos-Marcuse *et al.*, 2010, Christensen *et al.*, 2011, Marcus *et al.*, 2011, Kuo *et al.*, 2014, Lee *et al.*, 2014). Five studies reported that all identified trajectories were relatively stable over time, with average depression scores remaining either above or below the given symptom severity cut-point (Ramos-Marcuse *et al.*, 2010, Marcus *et al.*, 2011, Kuo *et al.*, 2012, Glasheen *et al.*, 2013, Kuo *et al.*, 2014). The remaining six studies reported a combination of stable and non-stable trajectories over time (Mora *et al.*, 2009, Christensen *et al.*, 2011, Vänskä *et al.*, 2011, Sutter-Dallay *et al.*, 2012b, Lee *et al.*, 2014, Parade *et al.*, 2014), also described as transient in Mora et al. (2009).

All studies reported either a low and/or a moderate-low stable symptom trajectory, and five studies reported both (Ramos-Marcuse *et al.*, 2010, Marcus *et al.*, 2011, Vänskä *et al.*, 2011, Kuo *et al.*, 2012, Kuo *et al.*, 2014). The low stable symptom trajectory is characterised by very low symptoms levels throughout the perinatal period, while the moderate-low stable trajectory is characterised by a higher level of symptoms that approaches but remains under the severity cut-off. Of the studies reporting either a low or a moderate-low stable trajectory (n = 6), this trajectory represented the majority of the sample in all studies (range 71.0% (Mora *et al.*, 2009) to 82.5% (Lee *et al.*, 2014)), but one (Glasheen *et al.*, 2013), where this trajectory represented a minority of the total sample (16.5%). The trajectory's sample size was not reported in Parade *et al.* (2014). Of the studies which reported both types of trajectories, the moderate-low stable trajectory tended to have a higher sample size than the low stable trajectory (Ramos-Marcuse *et al.*, 2010, Marcus *et al.*, 2011, Kuo *et al.*, 2012, Kuo *et al.*, 2014). An exception was the Vänskä *et al.* (2011) study, in which 75.5% of women were classified in the stable low trajectory, while only 8.7% were classified in the moderate-low stable trajectory.

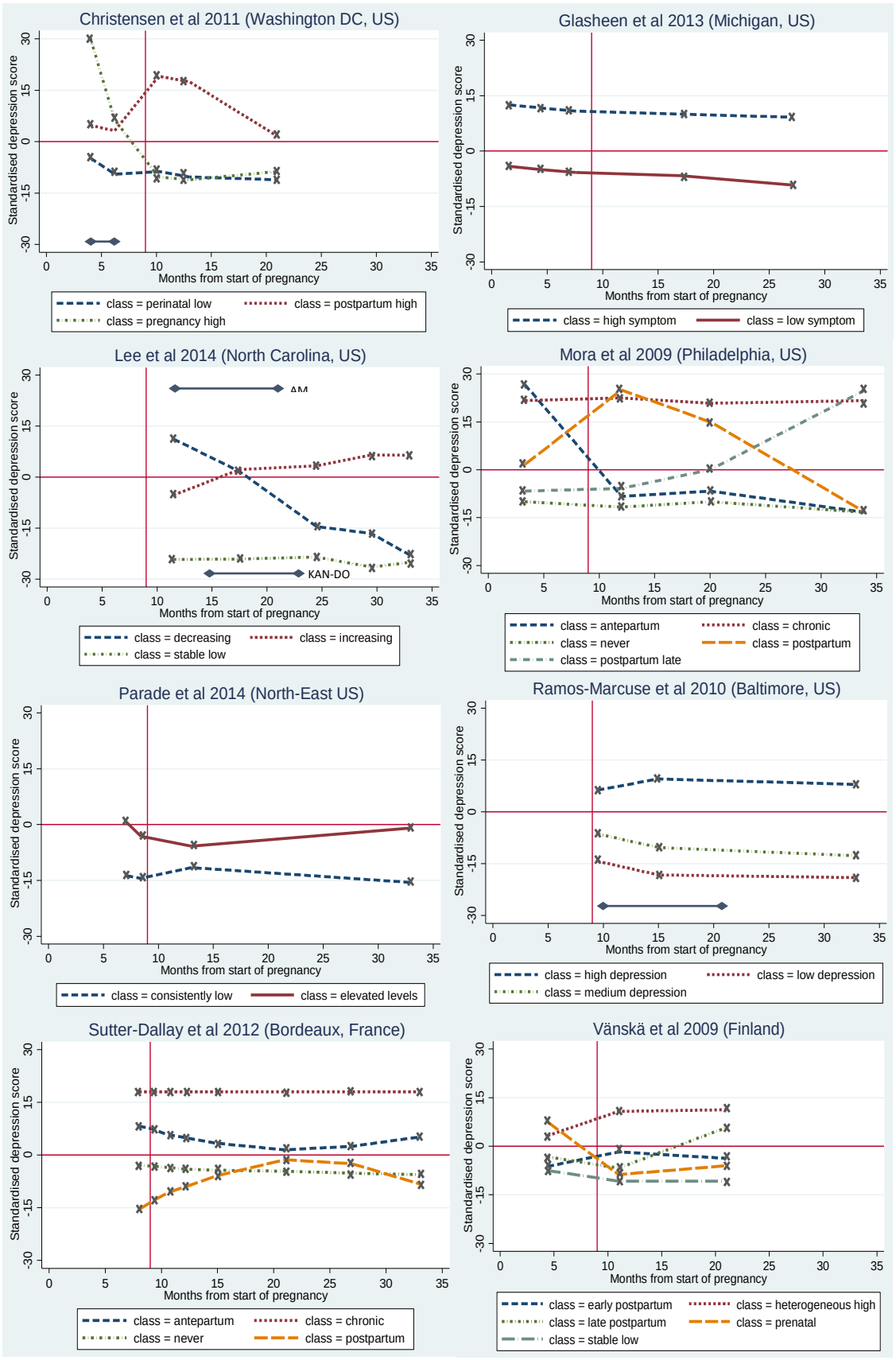

Figure 2.2 Standardised depressive symptoms over time for each trajectory, for studies with follow-up time beyond 6 months postpartum

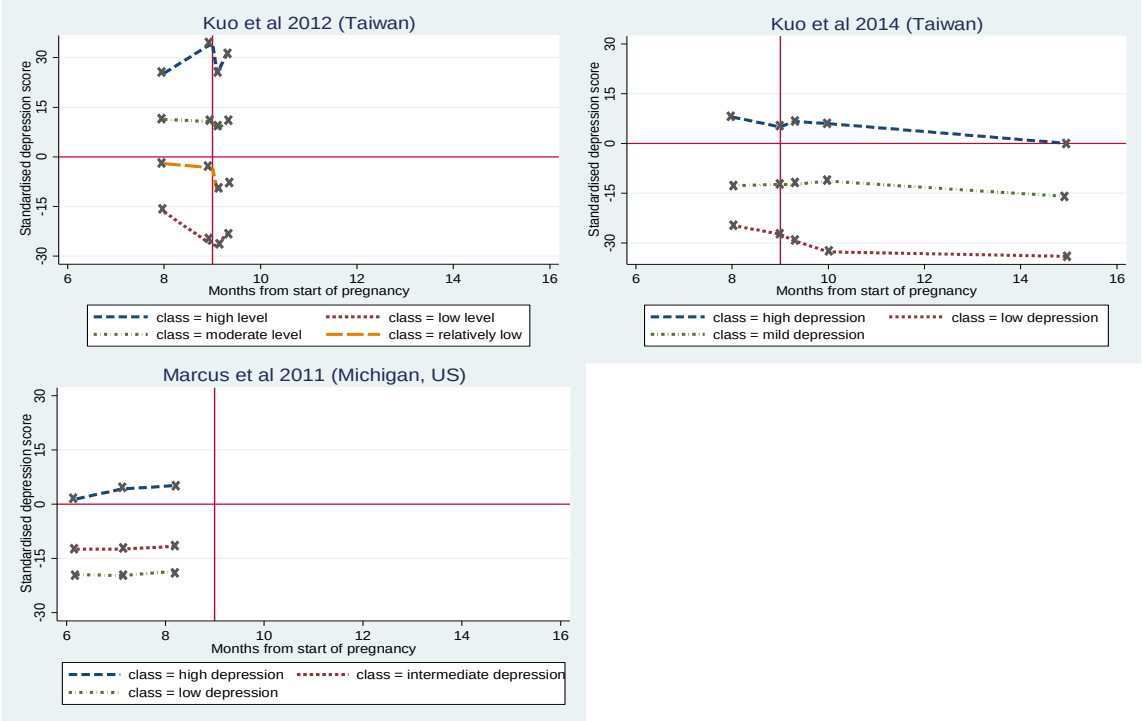

Figure 2.3 Standardised depressive symptoms over time for each trajectory, for studies with a maximum follow-up time of 6 months postpartum

A stable moderate-high and/or high symptom trajectory group was also reported by eight studies. Three studies reported identifying a trajectory with very high stable symptoms that represented a minority of the sample in all three studies: 8.3% of the sample in Kuo *et al.* (2012), 7% in Mora *et al.* (2009), and 3% in Sutter-Dallay *et al.* (2012b). Seven studies, including Kuo *et al.* (2012) and Sutter-Dallay *et al.* (2012b) reported a stable moderate-high symptom group, in which symptom levels hovered close to but above the severity cut-off, suggesting persistent but relatively less severe symptoms of depression. This trajectory represented the majority of the sample (83.5%) in Glasheen et al. (2013), but the minority of the sample in the remainder of the studies (range 4.2% (Vänskä *et al.*, 2011) to 27.3% (Kuo *et al.*, 2014)). In Vänskä *et al.* (2011), this trajectory exhibited substantial heterogeneity.

Six studies reported transient trajectories that can be grouped into three categories: increasing, decreasing or episodic. Four reported a decreasing trajectory, of which three were characterised by high symptoms during pregnancy, followed by a decline to low or mild levels in the postpartum period (Mora *et al.*, 2009, Christensen *et al.*, 2011, Vänskä *et al.*, 2011). The decreasing trajectory reported by Lee et al. (2014) was characterised by a steady decrease from the first six months postpartum to two years postpartum. This trajectory represented less than 10% of the samples in all four studies.

The increasing trajectory pattern, characterised by initially low depressive symptoms that increase to a level above the severity cut-off in the postpartum period, was reported by three studies (Mora *et al.*, 2009, Vänskä *et al.*, 2011, Lee *et al.*, 2014). A similar trajectory was reported by Sutter-Dallay *et al.* (2012b), but symptom levels ultimately remained under the depression severity cut-off. This trajectory also represented a minority of the total samples (range 4.0% (Sutter-Dallay *et al.*, 2012b) to 10.2% (Lee *et al.*, 2014)).

The third type of trajectory reported by three studies is characterised by episodic increases and decreases in depressive symptoms. In Christensen et al. (2011) and Mora et al. (2009), this trajectory begins with symptoms just above the cut-off that increase rapidly just after birth, but then return to levels either just above (Christensen *et al.*, 2011) or below the cut-off (Mora *et al.*, 2009). Nine percent (Mora *et al.*, 2009) and 10% (Christensen *et al.*, 2011) of women were classified in this trajectory. In Parade et al. (2014), the opposite episodic trajectory is reported: the trajectory begins above the severity cut-off in the third trimester of pregnancy, temporarily abates two weeks before birth, but increases again four weeks after birth and reaches the cut-off again by two months postpartum.

2.4.4. Factors associated with the trajectories

A total of nine studies investigated the association of baseline characteristics with membership in different trajectories of perinatal depressive symptoms (Table 2.5). All used the likelihood of being classified in the stable low or moderate-low depressive symptom trajectory (low-risk group) as the reference against which to compare the likelihood of being classified into other trajectories (Table 2.3). In Kuo *et al.* (2012), the stable low and moderate-low trajectories were combined into one trajectory, and the stable high and moderate-high were combined into a second trajectory, so that only these two groups were compared. For ease of reporting, these combined trajectories are considered stable low and stable high symptom trajectories, respectively.

Of the two studies that both reported low and moderate-low stable trajectories and investigated risk factors, one study found no differences between women assigned to either trajectory (Kuo *et al.*, 2014). The other only found that a greater proportion of the women assigned to the stable moderate-low trajectory were multiparous, compared to those assigned to the stable low trajectory (Vänskä *et al.*, 2011).

Table 2.4 Main findings of the 11 studies included in the systematic review

Study	Attrition rate	Classes	Trajectory labels and size	
Christensen et al (2011)	Not specified	3	1. Pregnancy high – high symptom levels antenatally, drops postnatally below risk cut-off (9.8%)	
			2. Postpartum high – near cut-off antenatally, marked increase postnatally, decrease to initial levels at 12 months postpartum (10.2%)	
			3. Perinatal low – never exceeds cut-off during pregnancy and postpartum period (80.0%)	
Glasheen et al (2013)	Range of follow-up rate: 76-82%	2	1. Low symptom group – low symptom levels, stable but small decrease over time (16.5%)	
			2. High symptom group – higher scores, stable but small decrease over time (83.5%)	
Kuo et al (2012)	One participant missing at first assessment, 7 missing at last assessment	4	1. Low levels of depressive symptoms antenatally, slight decrease in first three days after birth, slight increase one week after birth (23.1%)	Low-risk group
			2. Relatively low antenatally, slight decrease one day after birth and stabilises (43.0%)	
			3. Moderate stable levels antenatally and postnatally (25.6%)	High-risk group
			4. High scores antenatally, increases one day after birth, decreases 3 days after birth, slight increase to original levels at one week postpartum (8.3%)	
Kuo et al (2014)	All participants completed 4 assessments, 102 (73%) completed 5 assessments	3	1. Low depression – low levels stable over postpartum period (30.9%)	
			2. Mild depression – mild levels stable over postpartum period (41.7%)	
			3. High depression – high levels antenatally, slight decrease in first months postpartum, then stable (27.3%)	
Lee et al (2014)	Mean assessments: AMP: 2.5; KAN-DO: 1.86	3	1. Stable-low symptoms throughout postpartum period (82.5%)	
			2. Decreasing symptoms throughout postpartum period (7.3%)	
			3. Increasing symptoms throughout postpartum period (10.2%)	
Marcus et al (2011)	140 (91%) participants had at least 2 assessments	3	1. Low depression - low stable non-depressive during pregnancy (36.0%)	
			2. Intermediate depression - intermediate-stable depressive during pregnancy (56.0%)	
			3. High depression - high-elevated depressive during pregnancy (8.0%)	

Study	Attrition rate	Classes	Trajectory labels and size
Mora et al (2009)	More than 85% completed at least 2 assessments, 48% completed 4 assessments	5	1. Chronic – persistently high level of depressive symptoms antenatally and postnatally (7.0%)
			2. Antepartum - depressive symptomatology present only at first antenatal visit (6.0%)
			3. Postpartum – depressive symptoms present within 6 weeks of delivery, subsides over time (9.0%)
			4. Late – low levels of depressive symptoms antenatally, increase in second year postpartum (7.0%)
			5. Never – continuous low levels of depressive symptoms (71.0%)
Parade et al (2014)	Not specified	2	1. Consistently low levels of depressive symptoms antenatally and postnatally
			2. Elevated levels of depressive symptoms during pregnancy, temporary decline around birth, elevated again at 6 months postpartum
Ramos-Marcuse et al (2010)	82% did 2 assessments, 70% did all 3 assessments	3	1. Low depressive symptoms – stable low symptom levels (40.9%)
			2. Medium depressive symptoms - just below cut-off after birth, decrease over postpartum period, remain below cut-off at 6 months postpartum (45.3%)
			3. High depressive symptoms – symptom levels above cut-off which increase over the postpartum period (13.8%)
Sutter-Dallay et al (2012)	Not specified	4	1. Postpartum - lowest levels of the sample in third trimester, increase rapidly to reach maximum level at one year postpartum (4.0%)
			2. Never * – below cut-off with low decrease over postpartum period (72.0%)
			3. Antepartum – high average levels during pregnancy, decrease until one year postpartum (still above cut-off), increase slightly after that (21.0%)
			4. Chronic – stable high symptom levels from the end of pregnancy to 2 years postpartum (3.0%)
Vänskä et al (2011)	788 (98%) completed first assessment, 81.6% the second and, 67.7% the third; 65.7% completed all assessments	8 (4 + 4 combined in 1)	1. Stable low levels of mental health problems antenatally and postnatally (75.7%)
			2. Prenatal mental health problems (5.8%)
			3. Early postpartum mental health problems (8.7%)
			4. Late postpartum mental health problems (5.6%)
			5. Heterogeneous high levels of mental health problems (combined group of 4 classes) (4.2%)

The likelihood of belonging to a stable moderate-high symptom group (high, but close to cut-off) was higher among women who smoked more than a pack of cigarettes per day (Glasheen *et al.*, 2013), reported sleep difficulty in the third trimester and used patient-controlled analgesics after a caesarean section (Kuo *et al.*, 2014). Glasheen *et al.* (2013) also reported that women with high social support were 51% less likely to be in this group compared to those with low social support. In Sutter-Dallay *et al.* (2012b), the likelihood of being classified in this trajectory was greater for women who were older, nulliparous, reported a lower salary and had higher levels of trait anxiety. Vänskä *et al.* (2011), however, reported no demographic differences between the stable moderate-high and stable low trajectories during the perinatal period.

The likelihood of belonging to the stable high symptom trajectory compared to a stable low or moderate-low trajectory was higher for those who reported sleep difficulty in the third trimester (Kuo *et al.*, 2012). Mora *et al.* (2009) found a higher likelihood of belonging to this group among women who reported being white (vs. black), were multiparous, had fair or poor emotional health, were anxious about the pregnancy and showed moderate or high objective stress. Sutter-Dallay et al. (Sutter-Dallay *et al.*, 2012b) also reported a higher likelihood of belonging to that group among women who had higher trait anxiety levels.

In Mora et al. (2009), the likelihood of belonging to the transient, decreasing trajectory was greater for women who reported not being born in the country (US), self-identified as white (as opposed to Latina/Hispanic), rated their emotional health as fair or poor, had recently consumed alcohol, were anxious about the pregnancy, and reported a high level of objective stress (Mora *et al.*, 2009). Multiparous women (Vänskä *et al.*, 2011) and women with lower social support (Christensen *et al.*, 2011) also had a greater likelihood of belonging to this trajectory. Lee et al (2014), who identified a similar trajectory but only in the postpartum period, did not find any differences between women in this group versus those with stable low-level symptoms.

Lee et al (2014) did find differences for women who were classified in the transient, increasing trajectory compared to those in the stable low trajectory: postpartum women with increasing symptoms were less likely to report good physical health in the third trimester of pregnancy (Lee *et al.*, 2014). Mora *et al.* (2009) reported that the likelihood of belonging to this trajectory was also higher for women who had less than high school education and had higher levels of objective stress. No differences were found in the likelihood of being classified in this trajectory in comparison to the stable low trajectory in the other two studies reporting these trajectories (Vänskä *et al.*, 2011, Sutter-Dallay *et al.*, 2012b).

Table 2.5 Factors associated with the trajectories reported in the 11 studies included in the review

Study [a]	Stable				Transient		
	Low	Moderate low	Moderate high	High	Increasing	Decreasing	Episodic
1		Reference group				Lower social support	No health insurance History of abuse
2		Reference group	Lower social support Cigarette smoking (>1 pack a day)				
3	Reference group			Sleep difficulty in third trimester			
4	Reference group	*No associations*	Sleep difficulty in third trimester No patient-controlled analgesics				
5	Reference group				Poorer self-reported physical health	*No associations*	
6[b]	n/a	n/a	n/a				
7		Reference group		Ethnicity (white vs. Black non-Hispanic) Non-nulliparous Poor/fair self-rated emotional health Anxious about pregnancy Moderate/high objective stress	Education (<high school) Moderate/high objective stress	Not US-born Ethnicity (white vs Latina/Hispanic) Poor/fair self-rated emotional health Recent alcohol use Anxious about pregnancy High objective stress	Ethnicity (white vs. Black non-Hispanic) Parity (1-2 children) Education (≤ high school) Poor/fair self-rated emotional health Comorbid disorder Moderate/high objective stress
8	Reference group						Lower education Decreased remembered paternal care Conflict resolution strategies
9[b]	n/a	n/a	n/a				
10		Reference group	Older age Higher trait anxiety Lower income Nulliparous	Higher trait anxiety	*No associations*		
11	Reference group	Multiparity	No associations		*No associations*	Multiparity	

[a] 1 Christensen et al. (2011); 2 Glasheen et al. (2013); 3 Kuo et al. (2012); 4 Kuo et al. (2014); 5 Lee et al. (2014); 6 Marcus et al. (2011); 7 Mora et al. (2009); 8 Parade et al. (2014); 9 Ramos-Marcuse et al. (2010); 10 Sutter-Dallay et al. (2012); 11 Vänskä et al. (2011). [b] Risk factors not investigated in the study.

Finally, differences found between women assigned to the episodic trajectory in Mora *et al.* (2009) compared to those assigned to the stable moderate-low trajectory were similar to those found for women assigned to the stable high trajectory, in terms of parity, ethnicity, emotional health and objective stress. Women classified in this episodic trajectory were also more likely to report low educational attainment and having a comorbid condition, however anxiety about pregnancy was not associated with this trajectory (Mora *et al.*, 2009). Christensen et al (2011), who also report a similar episodic trajectory, indicate that women assigned to this trajectory were more likely to not have health insurance or to report a history of abuse. In Parade et al. (2014), where the episodic trajectory shows temporary decreased symptoms just before and after birth, results suggests that women who were classified in this trajectory were more likely to have a lower education and decreased remembered paternal care.

2.5. Discussion

The objective of this study was to systematically review the literature that has used GCMM to identify groups of women with different trajectories of depressive symptoms and associated risk factors over the perinatal period.

2.5.1. Summary of evidence

All 11 studies included in this review reported identifying at least one low-risk group, characterised by stable low or moderate-low symptoms of depression (associated with scores below the severity cut-off for the instrument) throughout the perinatal period. The majority of studies also reported a high-risk trajectory, in which stable high depressive symptoms persisted from pregnancy throughout the postpartum period. Six of the 11 studies identified transient trajectories, with either increasing, decreasing or episodic depressive symptoms occurring in the perinatal period.

A range of risk factors or predictors of trajectories were investigated in nine studies, using the characteristics of women assigned to the stable low symptom trajectory as a reference. Very few predictors differentiated trajectories. Anxiety or stress were reported by two studies as increasing the likelihood of belonging to the stable high symptom trajectory (Mora *et al.*, 2009, Sutter-Dallay *et al.*, 2012b), and lower education as increasing the likelihood of having episodic depressive symptoms (Mora *et al.*, 2009, Parade *et al.*, 2014). Results also suggest that, within the same study, many of the same factors were identified as increasing the chances of belonging to stable or transient trajectories, in comparison to stable low trajectories. This suggests that predictors could not necessarily

differentiate women with persistent low risk for depression from those who might eventually experience severe symptoms in the perinatal period, or differentiating women whose symptoms might abate naturally from those who will continue to have severe symptoms throughout the perinatal period.

While studies were consistent in identifying a low-risk trajectory, the size of the stable low or moderate-low symptom trajectory varied by study. Out of the 10 studies who provided sample sizes, these trajectories comprised the majority of the sample in nine studies. The fact that the stable moderate-low trajectory was a minority in Glasheen *et al.* (2013) is particularly striking, given that the only other trajectory identified in their model represented stable high symptoms. The inclusion criteria were relatively broad in this study, and the sample was not a high-risk group. The authors do indicate, however, that the women recruited were predominantly of low socio-economic status. The fact that none of the socio-demographic predictors differentiated the two trajectories suggest that the sample was homogeneous, and supports the idea that socio-economic status may explain the very high proportion of women being classified in the stable high trajectory. This supports previous evidence suggesting that income or socio-economic level is associated with a greater risk for depression (Lund *et al.*, 2010). This finding was not replicated by Ramos-Marcuse et al. (2010), however, where over 40% and 45% of low-income women were assigned to the low and moderate-low symptom level trajectories, respectively.

Three studies did not report a stable high or moderate-high symptom trajectory (Christensen *et al.*, 2011, Lee *et al.*, 2014, Parade *et al.*, 2014). In Christensen et al. (2011), this may have been due to the inclusion criterion which excluded all women who were already diagnosed with depression. This was however not seen in Marcus et al. (2011), who also excluded women with depression but still report a stable moderate-high trajectory. Also, symptoms were only assessed for several weeks during pregnancy, and a longer assessment period may have revealed trajectories similar to those found by Christensen et al. (2011).

The second study not reporting a stable high trajectory was Parade et al's (2014). This study was one of the three that were rated as 'low quality'; contributing to the low score was the vague inclusion criteria, the extremely small sample size, and the lack of reporting on the proportion of the sample classified in either trajectory. The small sample size may have limited the ability to identify a robust third trajectory class through GCMM. The third study without a stable high or moderate-high symptom trajectory was Lee *et al.* (2014), which investigated postnatal depressive symptoms among overweight or obese women. This is an interesting finding, given that the evidence suggests that obesity is a risk

factor for postpartum depression (Milgrom *et al.*, 2012, Marchi *et al.*, 2015). However, the lowest number of assessments per women was reported in this study, which is likely to have influenced the trajectories identified through GCMM.

The fact that depressive symptoms were investigated for various lengths of time pre- and/or postnatally may explain the variety of trajectories reported, and make it difficult to truly compare trajectories across studies. Indeed, many of the studies which investigated both antenatal and postnatal symptoms only did so for a few weeks during pregnancy (Kuo *et al.*, 2012, Sutter-Dallay *et al.*, 2012b, Kuo *et al.*, 2014, Parade *et al.*, 2014) and/or up to six or 12 months postpartum (Christensen *et al.*, 2011, Vänskä *et al.*, 2011, Kuo *et al.*, 2012, Kuo *et al.*, 2014). Yet, studies with longer follow-up periods show that symptoms can still increase or decrease substantially after the first year postpartum (Mora *et al.*, 2009, Sutter-Dallay *et al.*, 2012b, Lee *et al.*, 2014). Investigating depressive symptoms only during pregnancy or in the postpartum period also gives a partial picture of the change in mood from pregnancy to motherhood, especially given that both periods are hormonally and psychologically different. For example, in Lee's study (2014), the decreasing symptom trajectory from birth to two years postpartum may be similar to the 'postpartum' trajectory in Christensen et al. (2011) or Mora et al. (2009), where symptoms increased periodically around birth. Similarly, while Ramos-Marcuse et al. (2010) report only stable trajectories, the stable moderate-low trajectory identified could represent the postnatal part of the transient decreasing trajectory reported in another three studies (Mora *et al.*, 2009, Christensen *et al.*, 2011, Vänskä *et al.*, 2011). In other words, women assigned to low-risk trajectories in the postpartum period may have been at risk for depression antenatally, and vice versa.

Regular symptom assessments over a shorter period of time also have advantages, mainly in allowing more nuanced description of changes in symptom experiences. This is what Marcus et al. (2011) and Kuo et al. (2012) did, by examining depressive symptoms over two months during pregnancy and several days after birth, respectively. Both studies, however, report relatively stable symptoms, even in the first week after giving birth (Kuo *et al.*, 2012). It is common for women to develop depressive symptoms during the first two weeks after giving birth, often referred to as the 'baby blues', but this phenomenon was not reflected in Kuo et al. (2012) or Parade et al (2014)'s study. In fact, Parade *et al.* (2014) report an atypical trajectory of high levels of depressive symptoms during pregnancy and postnatally, with a temporary decrease immediately after birth. The authors referred to this as the 'honeymoon period'. None of the other studies included in this review examined depressive symptoms close enough to the birth of the baby to corroborate these findings. The existence of a 'honeymoon' period would have important implications on timing of screening and detection of 'postpartum blues' or postpartum depression. Interestingly, elevated mood levels were also reported

in earlier work by Glover *et al.* (1994), who reported mild hypomania, or 'Highs', in a small proportion of perinatal women in the first few days after giving birth. In their study, women reporting such symptoms were at increased risk of suffering from postpartum depression at six weeks postpartum. This further emphasizes the need to assess for depressive symptoms at regular and short intervals throughout the perinatal period, which is clearly lacking in the current evidence.

Findings from studies which report transient trajectories also have implications for timing of screening. While transient trajectories only represented a minority of the sample in each study, they often overlapped with stable low or high trajectories for several months (Mora *et al.*, 2009, Christensen *et al.*, 2011, Vänskä *et al.*, 2011, Sutter-Dallay *et al.*, 2012b). Further complicating the identification of women at risk for perinatal depression, results from this review indicate that few socio-economic predictors differentiate women who have chronically high symptom levels from those who have decreasing levels of symptoms (Mora *et al.*, 2009, Vänskä *et al.*, 2011). There is also mixed evidence on predictors differentiating women who have stable low levels of symptoms from those whose symptoms increase in the postpartum period (Mora *et al.*, 2009, Vänskä *et al.*, 2011). Indeed, in Mora *et al.* (2009) for example, while each trajectory could be differentiated from the stable moderate-low trajectory on a range of demographic and psychosocial factors, these predictors were similar across trajectories. Perhaps important distinctions were missed by conducting post-hoc multinomial analyses, which require that all trajectories be compared to one reference trajectory only, when comparisons of two transient trajectories, or comparison of stable high-symptom trajectory with a transient one may be more useful in this context.

The lack of demographic or socio-economic differences identified across different trajectories may be due to the homogeneity of the samples recruited, as a result of the strict inclusion criteria implemented in most studies in this review. For example, the fact that no differences were found between the stable low and stable high symptom trajectory classes in Glasheen et al's study (2013) may be due to the low variability of the socio-economic status of the women recruited. The lack of differences across trajectories may also be due to the relatively small samples reported in the studies reviewed. There are usually no restrictions on sample sizes for conducting GCMM; they usually depend on the number of parameters in the model, attrition and missing data, the instruments used, as well as on the distribution of variables. However, small samples can lead to an inability to identify smaller but meaningful latent trajectories (Berlin *et al.*, 2014), or to generate smaller trajectories, comprising of a sample too small to detect statistical differences in predictors between the trajectories.

Another possible reason for the lack of differences in characteristics across trajectories is the type of risk factors investigated in each study. Besides demographic factors that were investigated in most studies, risk factors examined mostly pertained to the emotional state of women (trait anxiety, stress, emotional health), their ambivalence about pregnancy, their self-esteem, or general health (physical health and sleep difficulty). Other common risk factors for perinatal depression, such as partner and social support, domestic violence, obstetric complications, as well as anxiety and traumatic life events (Robertson *et al.*, 2004, Lancaster *et al.*, 2010, Verreault *et al.*, 2014), should be investigated further in the context of GCMM analyses. Researchers should also be cognisant of the different effects risk factors have on depressive symptoms when investigating differences between trajectories. Indeed, one could argue that transient stressors, such as a traumatic life event, may have a more episodic effect on depressive symptoms over time, compared to persistent risk factors, such as community violence or poverty, which may have more permanent repercussions on depressive mood.

2.5.2. Limitations

A few limitations of the review should be noted. First, a small number of studies were identified, and none from low- and middle-income countries, despite the absence of publication date or language restrictions. This may be due to the fact that only studies using GCMM were included, and not all researchers investigating perinatal symptoms over multiple time points may have had the statistical expertise to use this analytical approach. However, only a minority of articles were excluded based on this criterion alone. Second, though one study investigated perinatal depressive symptoms among low-income women (Ramos-Marcuse *et al.*, 2010), most studies were conducted in urban settings, none were based in low or low-middle income countries, and, in general, studies' inclusion criteria were quite strict.. This speaks to the disadvantages of data-driven approaches, such as GMM, which depend on the distributions and variations of symptoms among the specific samples included in the studies, which are context- and time-specific. The extent to which results are generalisable across studies, or reflect something that is an inherent phenomenon, can only be assessed by comparing multiple studies across a wide variety of settings and populations. This is a clear limitation of the current literature reviewed, the findings of which are likely to be limited to low-risk women in middle- high income countries.

Third, important distinctions between trajectories may also have been missed by focusing on baseline characteristics only. In addition to predictors, investigating outcomes may give a better indication of whether different trajectories identify 'real' subgroups of women. Though this was beyond the current study's scope, it represents an important future direction of research. Finally, none of the articles

reported the parameters of the model identified, such as the slopes, intercepts, variances and co-variances of latent trajectories, and instead reported fit statistics used in the identification of the optimal model and number of latent trajectories. For this reason, a meta-analysis of the articles was not possible.

Limitations relating to latent growth mixture models and their interpretation must also be noted. First, the observed data (i.e. baseline risk factors or characteristics of women) are a function of the probability of belonging to certain trajectories in the growth curve mixture model, so any differences identified between trajectories in subsequent phases have a level of uncertainty, and do not capture the individual variability within each class. For these reasons, findings should be interpreted with caution, especially when, with attrition, less than three assessments on average are completed (Lee *et al.*, 2014) or when few fit statistics are used to select the optimal model (Marcus *et al.*, 2011, Kuo *et al.*, 2012). Two studies used only the BIC as the fit statistic to select the optimal model generated from the GCMM. While some researchers report that BIC is the most reliable criteria for identifying the optimal number of trajectories (Nylund *et al.*, 2007), others report that entropy, which indicates the extent to which an individual is classified into one latent group with confidence, is usually favoured over other fit indices (Ram and Grimm, 2009, Leiby, 2012). Also, the use of prospective data, rather than retrospective (secondary) data, such as is the case for several studies included in this review, also limits the interpretation of the findings since data are constrained by the original recruitment and data collection methods. Instead, prospective studies can be tailored to GCMM, by recruiting bigger samples, planning for at least 5 assessments, and having a clear plan about how to deal with missing data.

Others have also warned about creating trajectories when there is only one 'real' trajectory (Bauer and Curran, 2003). Indeed, a growth curve mixture model will generate a multiple-trajectory model, regardless of whether these trajectories have realistic benefits or implications for understanding the aetiology or progression of perinatal depression. Unnecessary trajectories could be generated due to non-normally distributed outcomes, inappropriate screening or measurement tools or even overly large samples (Ram and Grimm, 2009). Moreover, by using GCMM, researchers may run the risk of creating overly complex models that are difficult to interpret, or of creating overly simplistic models that ignore heterogeneity in the actual progression of symptoms among different subgroups of women. While this possibility cannot be ignored, the majority of studies included in this review did use extensively locally validated screening tools, and most often selected models with parsimony, all fit statistics being equal. Given the exploratory nature of GCMM, Ram and Grimm (2009) also suggest basing the identification of the optimal model on past research and theory as much as possible.

Authors of studies included in this review do acknowledge using theoretical and pragmatic interpretability to select optimal models, though they are not very explicit in stating which theories or interpretations these are. Future studies using this method could benefit from clearly stating the theoretical considerations taken into account, besides the fit statistics, when selecting optimal models.

Despite these limitations, the use of GCMM overcomes many of the limitations of other more common longitudinal data analyses, which, for example, create trajectory groups based on the number of times individuals score above a pre-defined threshold on a screening instrument. Thus, GCMM takes a more dimensional view of depression (Jacob and Patel, 2014, Patel, 2017), and allows researchers to identify subgroups of women with different profiles of depression, health risks and treatment needs. Findings generated through GCMM research are of direct clinical utility, as these could help tailor the timing and content of screening, thereby improving the efficiency of identification, referral, and treatment strategies, which is especially necessary in a context of limited mental health resources. The use of GCMM in the context of randomised controlled trials has also been advocated to identify whether response to the treatment under investigation differs across subgroups of women with perinatal depression. Bearing in mind the diverse trajectories of depressive symptoms during the perinatal period, evidence can be built for how, when and for whom psychosocial interventions are most likely to be effective. Having said that, GCMM remains a descriptive analytical tool, and should be used in combination with other longitudinal modelling strategies, such as structural equation modelling or multilevel modelling, which are more suited to identify factors involved in the aetiology of perinatal depression, and to understand pathways between depressive symptoms and child outcomes.

2.6. Conclusions

Bearing in mind the constraints of GCMM, this method has allowed researchers to identify heterogeneity in the course of perinatal depressive symptoms within populations. The studies included in this review report relatively similar types of depressive symptom trajectories during the perinatal period. The stable high symptom group consistently reported suggest that there is clearly an at-risk population of women, with strikingly persistent severe symptoms throughout the perinatal period. It is important for policy makers and providers to realise that severe symptoms may not necessarily abate on their own, and that not identifying and treating these women early is likely to result in a long period of distress and potential health risks for the mother and the child. This review also suggests that there is little information on how groups of women with transient or stable levels of depressive symptoms differ. It is unclear whether this finding is due to the relatively small samples recruited for this type of analysis, whether the trajectories generated are actually not meaningfully

different, or whether they are but they differ in ways that have not yet been measured. It is important that more high quality GCMM studies are completed, particularly with bigger samples, risk factor selection be guided by a theoretical framework, with clear reporting of all theoretical and practical steps taken. More consistency in assessment schedules throughout the perinatal period would also allow greater comparison of findings across studies. Only then will we be able to draw conclusions on the meaningfulness and clinical applicability of trajectories identified through GCMM, which is yet to be determined, and generate findings that will help improve the identification systems of at-risk perinatal women in clinical settings. More research should also focus on women living in LMIC. Identifying high-risk groups in settings where mental health services and resources are limited would allow screening and interventions to be focused on women with greater needs, thereby reducing the burden of service delivery.

Chapter 3. Trajectories and predictors among perinatal women at risk for depression antenatally in Khayelitsha

3.1. Brief overview

The aim of the study in this Chapter was to identify trajectories of perinatal depressive symptoms and their predictors among women living in a low-resource setting in South Africa who present with greater risk of depression during pregnancy. This is a secondary analysis of a randomised controlled trial among 384 low-income women living in Khayelitsha, South Africa. Participants were recruited at their first antenatal visit if they scored 13 or above on the Edinburgh Postnatal Depression Scale, were at least 18 years of age, less than 29 weeks pregnant and spoke isiXhosa. Participants were followed up at 8 months gestation, 3 and 12 months postpartum. Latent trajectories of depressive symptoms were identified using growth mixture modelling, based on the Hamilton Depression Rating Scale (HDRS). There were no significant differences in HDRS scores between the control and intervention arms, so all participants were assessed together. Health, social and economic predictors of trajectories were investigated to identify high-risk groups with greater or more chronic depressive symptoms. This was done using univariate logistic regression. Two trajectories were identified: *antenatal only* (91.4%), with moderate to severe symptoms at baseline which later subside; and *antenatal and postnatal* (8.6%), with severe depressive symptoms during pregnancy and later in the postpartum period, which subside temporarily to moderate levels at 3 months postpartum. Predictors for the *antenatal and postnatal* trajectory include severe food insecurity, intimate partner violence, lower social support, greater functional impairment, problematic drinking and suicidal risk. A small proportion of women who are at risk for depression antenatally remain at risk throughout the perinatal period, and can be differentiated from those who show a natural remission. Identification and referral strategies should be developed with these findings in mind, especially given the limited mental health resources in low-income settings.

3.2. Introduction

Depression during pregnancy and the postnatal period, known as perinatal depression, is a concern worldwide. In South Africa, the prevalence of women at high risk for depression or suffering from depression ranges between 21% and 39% antenatally (Hartley *et al.*, 2011, Manikkam and Burns, 2012,

Brittain *et al.*, 2015, Redinger *et al.*, 2017), and between 16% and 32% postnatally (Ramchandani *et al.*, 2009, Dewing *et al.*, 2013, Verkuijl *et al.*, 2014). The burden of disease associated with perinatal depression and impact on child health and development (Wachs *et al.*, 2009, Gelaye *et al.*, 2016) warrants further research to understand the disorder's aetiology, identify at-risk populations and develop effective preventive and therapeutic interventions.

The global evidence base on risk factors for perinatal depression is growing. Several factors have systematically been reported in low- and middle-income countries (LMICs) and high-income countries (HICs), such as a history of depression, social conflict, and lack of social support from family or partner (Lancaster *et al.*, 2010, Sawyer *et al.*, 2010, Fisher *et al.*, 2012, Biaggi *et al.*, 2016). Younger age, lower education status and being single are among the few demographic risk factors which have received some, but mixed evidence, for both antenatal and postnatal depression (Sawyer *et al.*, 2010, Fisher *et al.*, 2012, Biaggi *et al.*, 2016, Gelaye *et al.*, 2016). While evidence for socio-economic risk factors is mixed in South Africa (Brittain *et al.*, 2015, van Heyningen *et al.*, 2016, Redinger *et al.*, 2017), food insecurity, reported by 38% of households in South Africa (Sorsdahl *et al.*, 2011), has consistently been identified as a risk factor for antenatal and postnatal depression in the Western Cape (Tsai *et al.*, 2012, Dewing *et al.*, 2013, van Heyningen *et al.*, 2016, Abrahams *et al.*, 2018). Intimate partner violence (IPV) has also been reported as a risk factor for perinatal depression in South Africa (Brittain *et al.*, 2015, Groves *et al.*, 2015, Peltzer *et al.*, 2016, Schneider *et al.*, 2018), where IPV is common and is reported by more than 40% of pregnant women (Sowa *et al.*, 2015).

Few studies have focused on identifying health-related predictors of perinatal depression, yet these are particularly relevant in LMICs. The prevalence of HIV in South Africa is among the highest worldwide (UNAIDS, 2017), and perinatal depression is more common among HIV-positive women (Peltzer *et al.*, 2016). The rates of alcohol consumption per capita are also very high in South Africa (World Health Organization, 2014a): in recent studies conducted in low-income areas of Cape Town, 7.1% of women indicated problematic drinking at 8 months gestation (Davis *et al.*, 2017), and 16% reported hazardous drinking three months after giving birth (Dewing *et al.*, 2013). Evidence suggests an association between alcohol use during pregnancy and postpartum depression (Dewing *et al.*, 2013, Davis *et al.*, 2017), though none has been found with antenatal depression (Hartley *et al.*, 2011). The heterogeneity in risk factors identified for antenatal or postnatal depression highlight the complexity of this disorder's aetiology and course. The fact that most of the evidence is based on cross-sectional studies further limits our understanding of the factors associated with the onset, severity and chronicity of depressive symptoms during the perinatal period. Recent literature has used latent modelling techniques to investigate the heterogeneity of depression, both in terms of symptom

profiles and trajectories (Nandi *et al.*, 2009). Two systematic reviews have summarised the evidence using such modelling techniques in the context of perinatal depressive symptoms (Baron *et al.*, 2017, Santos *et al.*, 2017). Both reviews identified the most commonly reported trajectories to be a chronically severe and a chronically low symptom level trajectory. Transient trajectories were also reported, some of which suggested a natural remission among some women with initially severe levels of depressive symptoms antenatally (Mora *et al.*, 2009, Christensen *et al.*, 2011, Vanska *et al.*, 2011, Lee *et al.*, 2014). Baron *et al.* (2017) also point that predictors identified for several trajectories were not consistent across studies and did not distinguish women with chronic symptoms from those who presented transient trajectories.

Identifying such predictors would be especially useful in low-resource settings such as South Africa, since the use of screening instruments to identify women at risk for depression, without effective referral and treatment mechanisms, can overburden already weak and limited mental health services (Kagee *et al.*, 2013). Indeed, being able to identify women who are most likely to suffer from chronic symptoms from those whose symptoms may abate naturally with minimal intervention may help streamline referrals and help target women who are most at risk. Unfortunately, as both reviews highlight, there is a dearth of evidence from LMICs. Only one LMIC study was conducted, among West African perinatal women (Barthel *et al.*, 2017). The inclusion criteria meant, however, that the sample was a particularly low-risk group, and neither chronically severe or initially severe trajectories were identified. Given the gap in the literature, the aim of this study was to identify trajectories of perinatal depressive symptoms and their predictors among low-income South African women who were already at risk for depression during pregnancy.

3.3. Methods

3.3.1. Setting

This study is a secondary analysis of data collected for a randomised controlled trial (RCT) assessing the cost-effectiveness of a brief psychosocial intervention for perinatal depression among 425 pregnant women at risk for depression living in Khayelitsha, a peri-urban township settlement on the outskirts of Cape Town, South Africa (Lund *et al.*, 2014). The poor living conditions, high crime rates and population density of Khayelitsha resembles that of the other settlements in South Africa (Statistics South Africa, 2011a, b, 2018b). The psychosocial intervention did not have an effect on women's depressive symptoms (Lund *et al.*, Under review), and so both arms were combined into one

sample in the present study. The recruitment and data collection methods have been described previously (Lund *et al.*, 2014), and are briefly reviewed here.

3.3.2. Participants

Recruitment took place in two community health centres in Khayelitsha. Pregnant women were screened for depressive symptoms during their first antenatal clinic booking, using the Edinburgh Postnatal Depression Scale (EPDS; (Cox *et al.*, 1987)). The EPDS is a 10-item Likert-scale questionnaire assessing a range of depressive symptoms, such as anhedonia, somatic symptoms and suicidal ideation. Its internal structure was acceptable among isiXhosa-speaking women in Khayelitsha (De Bruin *et al.*, 2004). Another validation study, conducted in a township settlement in Johannesburg, suggests that a cut-off of 13 is optimal to indicate a risk for depression, with a sensitivity and specificity of 76.0% and 81.8%, respectively (Lawrie et al. 1998). Women who were at risk for depression (scored 13 or above on the EPDS), were at least 18 years of age, spoke isiXhosa, and were in their first or second trimester were eligible for enrolment. For this study, participants who died, who experienced a miscarriage, or whose baby died during the course of the study were excluded from the analyses (n = 42). Besides food insecurity, the baseline demographic, clinical or social characteristics of participants excluded from and included the analysis did not differ (Lund *et al.*, Under review).

3.3.3. Procedure

Once enrolled, participants were randomised into either a psychosocial intervention or enhanced usual care. The psychosocial intervention was provided by trained community health workers and consisted of six counselling sessions which included elements of psycho-education on depression and pregnancy, problem solving, behavioural activation and healthy thinking (Nyatsanza *et al.*, 2016). The enhanced usual care consisted of monthly phone calls for three months, where participants were asked a series of question relating to their health, suicidal risk and recent life events. Phone calls lasted no more than five minutes, and were conducted by two separate community health workers, who were trained to conduct the phone calls, but were not trained in counselling. More details about the interventions and training are provided in Lund *et al.* (2014). All participants received the same regular antenatal care available at the clinics, which typically involves medical management of pregnancy, HIV testing and Prevention of Mother to Child Transmission care. An assessment was conducted at recruitment, and then again at eight months gestation, and three months and 12 months after giving birth. This was done by two fieldworkers who were blind to the participants arm allocation.

3.3.4. Measurements

All assessments covered a range of mental health, health, social and economic measures (See Appendix D). The baseline assessment also included socio-demographic questions (Lund *et al.*, 2014). Only age, education and marital status were considered potential demographic predictors and included in the analyses, as these characteristics are routinely collected during the first antenatal visits in South Africa.

Mental health

Depressive symptoms were primarily assessed using Potts *et al.* (1990)'s 17-item version of the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Scores range from 0 to 54; a higher score suggesting greater symptom severity. A more structured isiXhosa version of the HDRS was developed for the RCT for use by non-clinicians. This adapted version was validated and showed good construct validity and internal consistency (Cronbach's Alpha = 0.74), and the inter-rater (0.97 to 0.98) and test-retest reliability (0.90) were excellent (Davies *et al.*, Under review).

The Mini International Neuropsychiatric Interview (MINI) 6.0 (Sheehan *et al.*, 1998) Major Depressive Episode and Suicidality modules were used to assess past and present depression and suicidality risk, respectively. The MINI 6.0 is a brief diagnostic interview which has been used as a gold standard in diverse populations, including among HIV-infected patients in South Africa (Lozano *et al.*, 2013, Murray *et al.*, 2013). Participants were considered at high risk for suicide if they scored 17 or more on the Suicidality module (Sheehan and Lecrubier, 2010).

Finally, the World Health Organization (WHO) Disability Assessment Schedule (WHODAS 2.0; 12-item) (Üstün, 2010) was used to determine the participants' level of impaired functioning. The item-response theory-based scoring was used, generating a score between 0 and 100, with greater scores suggesting greater impairment. The WHODAS 2.0 has good reliability and validity across cultures and population type (Üstün, 2010). The Cape Town Functional Assessment Instrument (FAI), developed specifically for and validated among pregnant and postnatal women in this study (Schneider *et al.*, 2015), was also used to measure functional impairment. It is a 10-item questionnaire, with responses ranging from "no difficulty" to "can never do the task". A "not applicable" option is also available, so total scores are calculated by dividing the sum of item scores by the number of items responded to. The total score ranges from 0 to 4, with a greater score suggesting greater impairment.

Health

Alcohol use was assessed using the Alcohol Use Disorder Identification Test (AUDIT) (Saunders *et al.*, 1993), a 10-item questionnaire, developed by the WHO, to identify alcohol misuse. Scores range from 0 to 40, with greater scores indicating greater alcohol misuse. The AUDIT has been used to assess alcohol consumption habits in both men and women in the Cape Town region (Kalichman *et al.*, 2007, Kalichman *et al.*, 2008). The recommended cut-off for heavy or binge drinking among women in South Africa is 5, based on a validation study among a nationally representative sample (Aalto *et al.*, 2009). HIV status was also recorded.

Social

The Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet *et al.*, 1988), a 12-item 7-point Likert Scale questionnaire, was used to assess perceived emotional support from family, friends and a special person. Overall scores range from 0 to 84, with higher scores suggesting greater perceived support. The scale has been validated in several LMICs (Eker and Arkar, 1995, Doku *et al.*, 2015), including high-school students in Cape Town, South Africa (Bruwer *et al.*, 2008, Rothon *et al.*, 2011). Subscale scores were also calculated. IPV was assessed by asking participants if they had experienced physical (e.g. kicked, slapped, beaten) or sexual abuse by their partner in the past three months.

Economic

The Household Food Insecurity Access Scale (HFIAS) (Coates *et al.*, 2006) is a 9-item questionnaire assessing three dimensions of food insecurity. It was previously used in a study among postnatal depressed women in Khayelitsha (Dewing *et al.*, 2013). The HFIAS score was binarised so that participants were either considered severely food insecure or not, as previously done (Dewing *et al.*, 2013, Maxwell *et al.*, 2014). A proxy for socio-economic status was also developed using multiple correspondence analysis, where economic variables and housing assets were analysed to create an asset-based score. This score was transformed into a binary variable indicating whether participants were in the lower (below median asset score) or higher wealth category (at or above median asset score) (Lund *et al.*, Under review).

Instruments which had already been translated and validated in isiXhosa in previous studies (such as the EPDS, MINI, AUDIT, FAI and HFIAS) were reviewed by a translator for accuracy. All other sections in the assessments were translated into isiXhosa and back-translated to English.

3.3.5. Analysis

Identification of trajectories

The first stage of the analysis, conducted in Mplus version 8 (Muthén and Muthén, 1998-2015), consisted of conducting growth mixture modelling (GMM), a method which combines growth curves with latent modelling. GMM allows investigators to explore groups of individuals with similar profile trajectories (classes) and allows for individual variability within latent classes. The HDRS scores from pregnancy to 12 months postpartum were used to create latent trajectories. This instrument, rather than the EPDS, was used as it more sensitive to change (Ballesteros *et al.*, 2007).

Scores on the HDRS did not differ significantly between the control and intervention arms at any assessment (Lund *et al.*, Under review), so participants from the two arms were analysed together. Attrition in the intervention arm (19.6%) was higher than that in the control arm (6.5%), but no differences were found in baseline characteristics between participants who were lost to follow-up and those who were followed-up. To account for differences in attrition, arm allocation was included as a covariate in all growth mixture models. Missing data were assumed to be missing at random and were dealt with using robust maximum likelihood estimation. This method does not impute data, but rather takes into account all non-missing data for each participant to provide a maximum likelihood estimate of the missing data, directly within the analysis model. To represent non-equidistant time points of assessments, factor loadings were fixed to 0, 0.3, 0.7 and 1.6, to represent assessments at baseline, and then 3 months, 7 months and 16 months after baseline; time in months was divided by 10 to avoid non-convergence of the models (Berlin *et al.*, 2014). An inspection of the individual data suggested heterogeneous, non-linear trends. Goodness of fit values generated from preliminary one-class (non-mixture) analyses indicated that a quadratic change function fitted the data best (Hu and Bentler, 1999), so a quadratic pattern was introduced in subsequent models (Table 3.1).

Table 3.1 Results of preliminary one-class (non-mixture) analyses

One-class (non-mixture) models	AIC	BIC	CFI	RMSEA	SRMR
Intercept only	8171.806	8177.461	0.000	0.303	0.408
Linear	7962.612	8006.069	0.079	0.265	0.170
Quadratic	7754.626	7813.885	0.996	0.025	0.021

CFI: Comparative Fit Index; RMSEA: Root Mean Square Error of Approximation; SRMR: Standardised Root Mean Square Residual; NOTE: Can conclude model fits the observed data well when: CFI>0.95, SRMR<0.08 and RMSEA<0.06; smaller AIC or BIC values also suggest better model fit

A series of mixture models were run, first assuming no variation within trajectory classes (intercepts and slope variance fixed at 0 – latent class growth analysis [LCGA]), and then allowing free estimates of means and variances for latent variables (GMM). Small and non-significant negative residual variances for HDRS scores at 12 months were dealt with by fixing the residual variance to a value close to 0 (Berlin *et al.*, 2014).

Selection of optimal model

Models with increasing number of classes were fitted against the data, and compared using standard statistical measures: the Bayesian Information Criterion (BIC) (Raftery, 1995), the Akaike Information Criterion (AIC) (Akaike, 1983) and entropy (Ramaswamy *et al.*, 1993). Priority was given to entropy in cases where fit indices between two models were relatively similar (Ram and Grimm, 2009). Given the relatively small sample size of the RCT, model solutions that included a class that comprised less than 5% of the sample were avoided. Average probability of class membership for each estimated class (posterior probability) were also used as a criterion for model fit. Successive models with different number of classes were compared using the Lo-Mendell-Rubin Test (LMRT) (Lo *et al.*, 2001) and Bootstrap Likelihood Ratio Test (BLRT) (McLachlan and Peel, 2004). Finally, the shape and theoretical interpretability of the trajectory classes were also taken into account. Once the optimal model was selected, participants were assigned to a latent trajectory class based on their highest posterior probability.

To assess whether the psychosocial intervention had an effect on latent trajectories generated by the GMM, a sensitivity analysis was also conducted by running an unadjusted GMM, this time including the arm variable within the GMM model, so that trajectories would be generated per arm (Muthén *et al.*, 2002, Leiby, 2012).

Identification of risk factors

In the second stage of the analysis conducted in Stata 14, each demographic, health, social and economic variable was entered as a single predictor in an unadjusted logistic regression, with class membership as the outcome. Risk ratios with 95% confidence intervals are reported. Univariate, rather than multivariate, analyses were preferable given that the objective of the study was to identify high-risk groups more likely to suffer from severe and chronic symptoms, rather than to understand the complex interactions of risk factors leading to chronic depressive symptoms.

Table 3.2 Baseline characteristics of the sample, by class

Variable	Total (N = 384)			Antenatal only (N = 351)			Antenatal & postnatal (N = 33)		
	n	%	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)
Demographic characteristics									
Age			27.2 (5.61)			27.0 (5.54)			28.7 (6.23)
Gestation			17.2 (5.71)			17.1 (5.74)			18.2 (5.31)
Education level									
Grade 0-11	225	58.6		203	57.8		22	66.7	
Grade 12 or more	159	41.4		148	42.2		11	33.3	
Marital status									
Lives with partner	130	33.9		119	33.9		11	33.3	
Doesn't live with partner	254	66.2		232	66.1		22	66.7	
Economic characteristics									
Employment									
Employed	177	46.1		161	45.9		16	48.5	
Unemployed/studying	207	53.9		190	54.1		17	51.5	
Socio-economic status									
Lower wealth	195	50.8		176	50.1		19	57.6	
Higher wealth	189	49.2		175	49.9		14	42.4	
Food status									
Not severely food insecure	272	70.8		255	72.7		17	51.5	
Severely food insecure	112	29.2		96	27.4		16	48.5	
Social characteristics									
Intimate partner violence [a]	50	13.0		41	11.7		9	27.3	
Overall social support			58.3 (12.91)			58.8 (12.56)			52.8 (15.3)
Social support from family			20.1 (5.70)			20.4 (5.48)			16.9 (6.97)
Social support from friends			16.0 (6.24)			16.0 (6.19)			15.3 (6.77)
Social support from special person			22.2 (4.75)			22.4 (4.57)			20.6 (6.18)
Physical & mental health characteristics									
Functioning (WHODAS)			29.8 (17.64)			28.9 (17.13)			39.3 (20.34)
Functioning (FAI)			0.8 (0.5)			0.8 (0.5)			1.2 (0.6)
Heavy drinking [b]	114	29.7		99	28.2		15	45.5	
HIV positive status [c]	112	30.1		100	29.3		12	38.7	
Current diagnosis of depression (MINI) [d]	157	40.9		136	38.8		21	63.6	
Past diagnosis of depression (MINI) [d]	122	31.8		104	29.6		18	54.6	
High suicidal risk (MINI) [d]	68	17.7		57	16.2		11	33.3	

[a] reference is no IPV; [b] reference is no heavy drinking; [c] reference is HIV negative status; [d] reference is absence of diagnosis/risk.

3.3.6. Ethical considerations

The present study received ethical approval from the University of Cape Town Human Research Ethics Committee (HREC) (REF 835/2015), as did the randomised controlled trial on which this analysis is based (HREC REF 226/2011) (see Appendix E).

3.4. Results

3.4.1. Overview of sample

The characteristics of the sample at baseline are presented in Table 3.2. Overall, the sample presented a typical profile of women attending MOUs in Khayelitsha. For instance, participants were on average 27 years of age (SD = 5.56); the majority of participants reported not finishing high school (n = 225, 58.6%), not living with a partner (n = 254, 66.2%), and were not employed or still studying (n = 207, 53.9%). Over a quarter reported being severely food insecure (n = 112, 29.2%). A similar proportion reported being HIV-positive (n = 112, 30.1%) and drinking heavily during pregnancy (n = 114, 29.7%). Over 40% (n = 157) were diagnosed with current depression on the MINI, 17.7% (n = 68) were considered at risk for suicide, and 31.8% (n = 122) had a history of depression. The mean number of assessments conducted was 3.5: 65.6% (n = 252) of participants received all four assessments, 22.4%% (n = 46) received three assessments, and only 12.0% (n=46) received one or two assessments.

3.4.2. Identification of trajectories

Table 3.3 provides the fit information criteria of the models generated through LCGA and GMM. Smaller values of BIC and AIC suggest a better model fit, while entropy values closest to 1 suggest better classification. Models generated through GMM fitted the data better than the LCGA models. Fit indices indicated that a 2-class model was optimal (BIC = 7797.269; AIC = 7722.207), with an entropy (0.816) above the suggested minimum of 0.8 (Muthén *et al.*, 2009). The 3-class model had a slightly lower AIC value (7708.730) and generated a small but relevant class. However, the entropy was lower, and the model fit not significantly improved from the 2-class model according to the LMR and BLR tests. Taking these into consideration, and for reasons of parsimony, the 2-class model was selected.

Table 3.3 Latent class growth analysis and growth mixture modelling: comparisons of models

Classes	BIC	AIC	Entropy	Size (%) of smallest class	LMRT statistic (p-value)	BLRT statistic (p-value)
Quadratic LCGA [a]						
2	7825.996	7770.687	0.742	26.0	203.838 (<0.001)	-3977.544 (<0.001)
3	7809.547	7738.435	0.750	4.6	38.630 (0.034)	-3871.344 (0.030)
4	7817.215	7730.301	0.718	4.6	15.483 (0.304)	-3851.218 (0.288)
5	7828.413	7725.696	0.584	3.9	12.097 (0.657)	-3843.151 (0.647)
Quadratic GMM [b]						
2	**7797.269**	**7722.207**	**0.816**	**8.6**	**38.789 (<0.001)**	**-3862.313 (<0.001)**
3	7799.594	7708.730	0.807	4.2	20.612 (0.503)	-3842.104 (0.488)
4	7814.876	7708.209	0.762	1.6	8.177 (0.234)	-3831.365 (0.229)
5	7822.705	7700.235	0.771	1.3	15.330 (0.123)	-3827.105 (0.115)

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; BLRT= Bootstrap Likelihood Ratio Test; LMRT=Lo-Mendell-Rubin Test; [a] Latent curve growth analysis; [b] growth mixture modelling

The mean HDRS scores of women allocated to the two classes are presented in Figure 1. The *antenatal only* class is characterised by moderate levels of depressive symptoms at recruitment (mean = 15.0, SD = 4.28), which decrease steadily over pregnancy and early postpartum, then stabilise by 12 months postpartum (mean = 9.3, SD = 3.82). The majority of the sample were allocated to this trajectory (n = 351, 91.4%). The *antenatal and postnatal* class represents a minority (n = 33, 8.6%) with symptom levels above the recommended clinical cut-off of 17 (Zimmerman *et al.*, 2012) at recruitment (mean = 22.1, SD = 4.67), which decline to moderate levels until 3 months postpartum (mean = 12.9, SD = 5.40), but worsen again at 12 months postpartum to reach a mean of 19.3 (SD = 3.49).

Results of the sensitivity analysis, not presented here, suggest that a 2-class model per arm was the most optimal (Appendix F). The trajectories and sample proportions generated for each arm were similar to those presented when both arms were combined (Appendix G).

3.4.3. Predictors of trajectories

The results of the unadjusted logistic regressions are presented in Table 3.4. The *antenatal only* class was used as the reference class. None of the demographic variables differed between the two classes. Also, neither employment nor socio-economic status were significant predictors of class, however food insecurity was: the risk of being classified in the *antenatal and postnatal* trajectory among participants who reported being severely food insecure was 2.3 times as high as the risk of being classified in this trajectory among participants who did not report being food insecure (95%CI: 1.20, 4.36; p = 0.012).

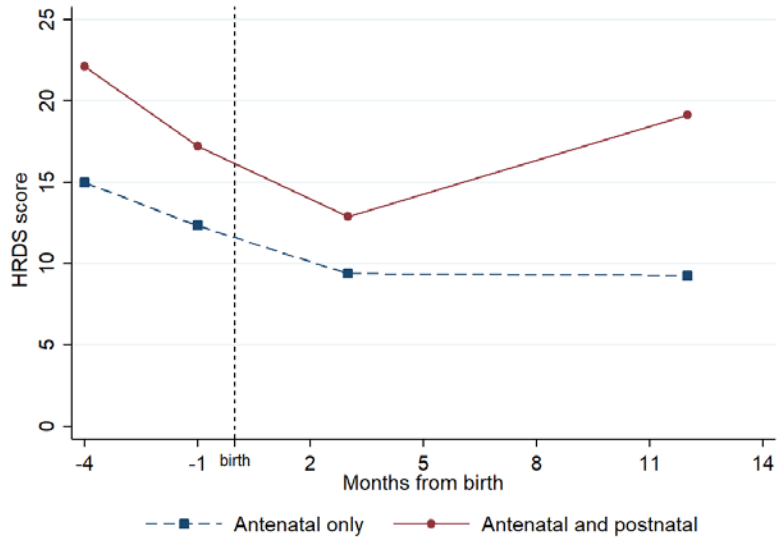

Figure 3.1 Mean HDRS curves of the GMM 2-class solution

Note: Missing data for *antenatal only* trajectory: 8 months gestation (n=84, 23.9%), 3 months postpartum (n=43, 12.3%) and 12 months postpartum (n=61, 17.4%); missing data for *antenatal and postnatal* trajectory: 8 months gestation (n=10, 30.3%), 3 months postpartum (n=4, 12.1%) and 12 months postpartum (n=3, 9.1%).

Participants with greater overall levels of social support had a lower risk of belonging to the *antenatal and postnatal* class compared to those with lower levels of social support (RR = 0.97, 95%CI: 0.95, 0.99; p = 0.008). However, only participants with greater level of family support (RR = 0.92, 95%CI: 0.88, 0.97; p = 0.001) or greater level of support from a special person (RR = 0.94, 95%CI: 0.89, 1.00; p = 0.035) were at greater risk of being classified in the *antenatal and postnatal* class. Those who reported experiencing IPV at baseline also had 2.5 times the risk of belonging to the *antenatal and postnatal* class compared to those who didn't report IPV at baseline (95%CI: 1.24, 5.08; p = 0.011).

Besides a HIV-positive status, all other health-related characteristics were associated with class membership: the risk of belonging to the *antenatal and postnatal* class was were greater among participants reporting greater functional impairment, measured with the WHODAS (RR = 1.03, 95%CI: 1.01, 1.05; p = 0.001) and FAI (RR = 5.35, 95%CI: 4.25, 6.73; p < 0.001); the risk was also greater among participants who reported heavy drinking during pregnancy (RR = 1.97, 95%CI: 1.03, 3.78; p = 0.040), had a current (RR = 2.53, 95%CI: 1.28, 4.99; p = 0.007) or past diagnosis of depression (RR = 2.58, 95%CI: 1.34, 4.94; p = 0.004), and were at high risk for suicide (RR = 2.32, 95%CI: 1.18, 4.56; p = 0.014).

Table 3.4 Unadjusted logistic regression, with antenatal only class as reference

	Antenatal & Postnatal (N = 33)		
Variable	RR	95%CI	p value
Demographic characteristics			
Age	1.05	0.99-1.11	0.104
Education level			
Grade 0-11	ref	-	
Grade 12 or more	0.71	0.35-1.42	0.329
Marital status			
Lives with partner	ref		
Doesn't live with partner	1.02	0.51-2.05	0.947
Economic measures			
Employment			
Employed	ref		
Unemployed/studying	0.91	0.47-1.74	0.773
Socio-economic status			
Lower wealth	ref		
Higher wealth	0.76	0.39-1.47	0.416
Food status			
Not severely food insecure	ref		
Severely food insecure	2.29	1.20-4.36	0.012
Social characteristics			
Intimate partner violence (IPV) [a]	2.51	1.24-5.08	0.011
Overall social support	0.97	0.95-0.99	0.008
Social support from family	0.92	0.88-0.97	0.001
Social support from friends	0.98	0.93-1.03	0.491
Social support from special person	0.94	0.89-1.00	0.035
Health characteristics			
Functioning (WHODAS)	1.03	1.01-1.05	0.001
Functioning (FAI score)	5.35	4.25-6.73	<0.001
Heavy drinking [b]	1.97	1.03-3.78	0.040
HIV positive status [c]	1.47	0.74-2.92	0.276
Current diagnosis of depression (MINI) [d]	2.53	1.28-4.99	0.007
Past diagnosis of depression (MINI) [d]	2.58	1.34-4.94	0.004
High suicidal risk (MINI) [d]	2.32	1.18-4.56	0.014

[a] reference is no IPV; [b] reference is no heavy drinking; [c] reference is HIV negative status; [d] reference is absence of diagnosis/risk.

3.5. Discussion

The aim of this study was to identify different trajectories of perinatal depressive symptoms and their predictors among low-income South African women at risk for depression antenatally. Through GMM, we were able to identify two subgroups of women with different severity and chronicity of perinatal depressive symptoms: an *antenatal only* trajectory and an *antenatal and postnatal* trajectory. On the one hand, the *antenatal only* trajectory is consistent with previous longitudinal studies reporting a natural remission group (Mora *et al.*, 2009, Christensen *et al.*, 2011, Vanska *et al.*, 2011, Lee *et al.*, 2014). This means that, without intervention, and despite initially mild to moderate symptoms during the first or second trimester, the majority of women showed improvements in their depressive

symptoms throughout the remainder of the perinatal period. The *antenatal and postnatal* trajectory, on the other hand, suggests that there was a minority of women who did not see their symptoms remit naturally and remained at risk for depression for most of the perinatal period. Both trajectories showed an initial decline in symptom severity, however, which suggests that screening within the first weeks after birth to identify women at risk for postnatal depression, as defined by the DSM-V and ICD-11 classifications, may not be effective in identifying at-risk women later in the postpartum period.

The findings also suggest that women who are at risk for chronic depressive symptoms can be differentiated from those showing a natural remission on a range of psychosocial and health-related characteristics during pregnancy, other than their initial depressive symptom severity. Women were at higher risk of belonging to the *antenatal and postnatal* class when they reported being severely food insecure, experienced physical or sexual IPV, had lower support from family or special person and reported problematic drinking during pregnancy. Women belonging to this trajectory were also at higher risk of suicide and were more likely to have received a diagnosis, either before or during pregnancy. These findings support previous evidence of the association between perinatal depressive symptoms in South African women and suicidal risk (Rochat *et al.*, 2013a), hazardous drinking (Dewing *et al.*, 2013, Davis *et al.*, 2017), IPV (Brittain *et al.*, 2015, Peltzer *et al.*, 2016, Schneider *et al.*, 2018) and food insecurity (Tsai *et al.*, 2012, Dewing *et al.*, 2013, van Heyningen *et al.*, 2016, Abrahams *et al.*, 2018).

Women who were more likely to suffer from chronic depressive symptoms therefore seem to have presented with a higher risk profile during pregnancy in terms of social, economic, health and mental health characteristics. This has important implications on referral and treatment procedures in settings where there are limited mental health resources. Given the greater likelihood of women diagnosed with depression to be allocated to the *antenatal and postnatal* trajectory, our findings indicate how effective a diagnosis would be in detecting women at higher risk, in settings where mental health resources are available. A perhaps more efficient use of mental health resources, especially when limited, could be for a mental health professional to conduct a formal diagnostic assessment in a stepped care manner, that is only among women who screened positive on a screening instrument (Araya *et al.*, 2003, Patel *et al.*, 2010). Alternatively, food insecurity, alcohol use during pregnancy and social support are factors which are relatively easy to assess during pregnancy. Thus, where mental health services are scarce, referrals to mental health professionals could potentially be limited to women with severe symptoms and who also present with greater functional impairment, or who report alcohol use or low support during pregnancy. Women with milder symptoms, who do not present a risk of experiencing chronic severe symptoms could instead be

referred to community-based support groups or to counselling by non-specialist health care workers; what is commonly known as task-sharing. Further research is required, however, to support these findings.

It is important to note that, despite a decrease in symptoms among the *antenatal only* trajectory, symptom levels remained within the mild range, albeit at the lower end (Zimmerman *et al.*, 2012) throughout the postpartum period. Yet studies have shown that chronic symptoms, even if mild or moderate, can have adverse effects on child outcomes (Santos *et al.*, 2017). It was beyond the scope of this study to assess whether women in different trajectory groups reported different child and maternal outcomes, however future studies should consider investigating the long-term effects of chronic trajectories on mother and child health in LMICs, across all levels of severity.

It is difficult to compare the present findings to those reported by Barthel *et al.* (2017)'s, the only other study using GCMM methods to assess perinatal depressive symptoms among women living in two LMICs. In their study of West African perinatal women, the authors are likely to have excluded a high-risk group by excluding women whose children were born prematurely or had a low birth weight from their study. This is supported by the fact that a chronically severe trajectory was not identified in their study, despite this trajectory being commonly reported in most studies using GCMM (Baron *et al.*, 2017). Instead, three trajectories were reported: a chronically low-symptom trajectory, and two transient trajectories, characterised by severe symptoms either early or late in the postpartum period, before returning to low levels (Barthel *et al.*, 2017). This supports previous studies, which have reported trajectories with initially low levels of depressive symptoms early in pregnancy, which increase later in the perinatal period (Mora *et al.*, 2009, Sutter-Dallay *et al.*, 2012a). It is therefore vital that future studies include women with a range of symptom levels at recruitment, to ensure that all potential trajectories and associated predictors be identified.

3.5.1. Limitations

The study provides useful evidence on the different trajectories of depressive symptoms of women at risk for depression at their first antenatal visit. However, several limitations need to be highlighted. First, the level of uncertainly associated with the predicted trajectory membership was not controlled for in the post-hoc analyses, which instead treated trajectories as an observed variable. The entropy was above the usual cut-off of 0.80, however, suggesting adequate classification of participants and considered sufficient to conduct post-hoc regression analyses (Muthén *et al.*, 2009). Also, with a

greater sample size, the three-class model identified through GMM may have been more optimal and more representative of the course of symptoms among low-income high-risk women in this setting.

Finally, it was established that the reduction in symptoms among the antenatal and postnatal trajectory was unlikely to be due to the psychosocial intervention assessed through the RCT. Indeed, there was no significant difference in HDRS scores at any point between the control and treatment arms, and the allocation arm was controlled for in the growth mixture model. The sensitivity analysis also revealed that the optimal model generated through GMM was similar when trajectories were generated per allocation arm. However, it is possible that the trajectories identified in this study may partly reflect the combined effect of the enhanced usual care and psychosocial interventions. Indeed, it has previously been suggested that the lack of difference between control and intervention arms, a common phenomenon of RCTs assessing behavioural interventions, may be due to the enhanced usual care having an effect on participants in the control arm, rather than a lack of effect of the intervention itself (Gold *et al.*, 2017). Further studies should run the same analyses among women at risk for depression but who did not receive any intervention.

3.6. Conclusions

This study is one of first studies to investigate the severity and course of depressive symptoms during the perinatal period using GMM in a LMIC. Despite the limitations highlighted above, the findings indicate that perinatal women at risk for depression antenatally cannot be considered as a uniform group. The findings highlight the importance of moving beyond a symptom-based identification of mental illness and towards a screening procedure that takes into account the importance of psychosocial determinants in the development and the course of perinatal depressive symptoms. By doing so, referral systems, as well as timing and target populations for interventions addressing perinatal depressive symptoms can be established in a more efficient way, given the limited mental health resources in low-income South African settings and in other LMICs.

Chapter 4. Trajectories and child outcomes among perinatal women in Khayelitsha

4.1. Brief overview

In this Chapter, latent modelling was used to identify trajectories of depressive symptoms among low-income perinatal women in South Africa. Predictors of trajectories and the association of trajectories with child outcomes were assessed. This is a secondary analysis of data collected among women living in Cape Town settlements (N = 446). Participants were eligible if pregnant and 18 years or older; they were included in the analysis if allocated to the control arm (routine perinatal care). Participants were excluded in case of non-singleton birth and baby death. Follow-up assessments were at two weeks, 6, 18 and 36 months postpartum. Trajectories of depressive symptoms were based on the Edinburgh Postnatal Depression Scale scores until 18 months postpartum, using latent class growth analysis. Child physical, cognitive, socio-emotional and behavioural outcomes were assessed at 18 and/or 36 months. Univariate and multivariate regressions were used to identify predictors of trajectories and differences in child outcomes. Four trajectories were identified: *chronic low* (71.1%), *late postpartum* (10.1%), *early postpartum* (14.4%) and *chronic high* (4.5%). Low social support, unwanted pregnancy and risky drinking were associated with the *chronic high* trajectory; unemployment and HIV-positive status with the *early postpartum* trajectory; and intimate partner violence with the *late postpartum* trajectory. Weight-to-length and weight-for-age z-scores at 18 months, and weight-for-age z-scores, length-for-age z-scores, emotional symptom and peer problem scores at 36 months differed across trajectories. Severe depressive symptoms in the postpartum period have a lasting effect on child physical and socio-emotional outcomes. Multiple screening throughout pregnancy and one year postpartum is essential.

4.2. Introduction

Perinatal depression, broadly defined by the World Health Organization (WHO) as major depression occurring during pregnancy and the first postpartum year, is experienced by 13% of women living in low- and middle-income countries (LMICs) (Woody *et al.*, 2017). Prevalence in South Africa has consistently been greater, with depressed mood experienced by 21% to 39% of women antenatally (Hartley *et al.*, 2011, Rochat, 2011, Manikkam and Burns, 2012, Brittain *et al.*, 2015, van Heyningen *et*

al., 2016, Redinger *et al.*, 2017), and by 24% to 35% of mothers postnatally (Cooper *et al.*, 1999, Ramchandani *et al.*, 2009, Verkuijl *et al.*, 2014). Extensive research has been conducted to document the effects of perinatal depression on children's health and development, most of which stems from high-income countries (HICs) and concentrates on socio-emotional and cognitive development (Goodman *et al.*, 2011, Kingston *et al.*, 2012, Kingston *et al.*, 2015, Liu *et al.*, 2017).

In LMICs, evidence has instead largely focused on physical outcomes, such as child physical growth, which is a key indicator of children's health and nutritional status (Parsons *et al.*, 2012). This is reasonable, given that in LMICs poor growth, malnutrition and infections are the leading causes of under-five mortality (Black *et al.*, 2010, Walker *et al.*, 2012). The majority of evidence comes from South Asia, however, and remains mixed in Sub-Saharan Africa (Gelaye *et al.*, 2016, Surkan *et al.*, 2016). There is emerging evidence on the impact of perinatal depression on emotional and behavioural development in LMICs (Gelaye *et al.*, 2016). In a South African birth cohort study, there was an association between high maternal depressive symptoms at six months postpartum and greater externalising problems among two-year old children (Avan *et al.*, 2010). However, no associations were found between severe antenatal depressive symptoms and social withdrawal at 10-12 months postpartum among HIV-infected mothers and infants in Cape Town (Hartley *et al.*, 2011). Finally, an association was found between postnatal depression at 2 months and insecure infant attachment at 18 months postpartum in a study conducted in a peri-urban settlement near Cape Town (Tomlinson *et al.*, 2006).

Most studies are cross-sectional, however, or include only one assessment of depressive symptoms, thus ignoring the complex and episodic nature of the disorder or the possibility that symptoms are a continuation of pre-pregnancy depression (Banti *et al.*, 2011, Martini *et al.*, 2015). Such methods have led researchers to ignore the importance of symptom chronicity (Kingston *et al.*, 2012, Stein *et al.*, 2014), and instead identify 'sensitive' periods, during which depressive symptoms are thought to have especially detrimental effects on child development (Woolhouse *et al.*, 2016, Liu *et al.*, 2017).

Emerging evidence from longitudinal studies in HICs and LMICs indicates that chronicity of depression is more important in predicting poorer child outcomes than are timing or severity of depression (Sohr-Preston and Scaramella, 2006, Stein *et al.*, 2014). For example, Rotheram-Fuller et al (2018)'s study in South Africa indicated that there is a greater risk of stunting, and increased internalising and externalising problems among children of mothers with chronic symptoms, but not among mothers whose symptoms were only present during pregnancy or only postnatally (Rotheram-Fuller *et al.*, 2018). Chronicity is usually measured as the number of times women screen positive on a depression

instrument over the course of a study. Because severe episodes are more likely to last longer, it has been argued that this way of conceptualising chronicity is flawed, as it confounds severity with chronicity (Pettit *et al.*, 2009, Prenoveau *et al.*, 2017). Also, it relies on an arbitrary cut-off for risk of depression, which can vary by population and measurement tool used.

Studies which have used more complex longitudinal analyses, such as growth curve mixture modelling (GCMM), have enabled the identification of latent subgroups of women with both chronic and transient symptom trajectories during the perinatal period, in both HICs (Baron *et al.*, 2017) and LMICs (Barthel *et al.*, 2017)(Chapter 3). This allowed investigators to disentangle severity from chronicity and moving away from the dichotomisation of depressive symptoms. Several studies, mostly from HICs have also made use of this modelling technique to compare child outcomes across different trajectories (Santos *et al.*, 2017). Overall, studies indicated that children of mothers experiencing severe or subclinical chronic depressive symptoms were more likely to have developmental problems, compared to children of mothers with severe, but transient, symptoms.

More research is needed in LMICs, where the course of perinatal depressive symptoms and the patterns of risk and resilience among children of mothers with perinatal depression may differ from HICs, given the contexts of food insecurity, HIV, violence, and increased risk of illness among children (Kingston *et al.*, 2012, Parsons *et al.*, 2012, Herba *et al.*, 2016). The aim of the present study was therefore to address this gap. With the use of a person-centred latent approach to identify different depressive symptom trajectories among low-income women in South Africa, this study's objectives were first to identify predictors of different trajectories, and second, to assess whether children of mothers with different trajectories showed different physical, cognitive, socio-emotional and behavioural outcomes at 18 and 36 months of age.

4.3. Methods

4.3.1. Design

This study is a secondary analysis of data collected as part of a cluster randomised controlled trial (RCT) among pregnant women living in peri-urban settlements in Cape Town, South Africa (Rotheram-Borus *et al.*, 2011). The aim of the cluster RCT was to assess the effect of a perinatal counselling intervention on a range of maternal and child health and nutrition outcomes. In already published work, the intervention did not have any effect on the participants' depressive symptoms (le Roux *et al.*, 2013, Rotheram-Borus *et al.*, 2014). However, some differences in child physical outcomes and

mothers' health behaviour were found between the two arms among depressed participants (le Roux *et al.*, 2013, Tomlinson *et al.*, 2015a, Tomlinson *et al.*, 2016). Therefore, only participants in the control arm were considered in this analysis. Data collection methods were described previously (Rotheram-Borus *et al.*, 2011), but are briefly summarised here.

4.3.2. Setting and randomisation

Forty neighbourhoods among three peri-urban settlements were selected as recruitment areas. With the use of aerial maps, street intercept surveys and street observation, 26 neighbourhoods were paired based on several characteristics, such as number of households, distance to an antenatal clinic, type of housing and sanitation. The remaining neighbourhoods were excluded due to variability on these criteria. Neighbourhoods in matched pairs were randomised into the control or intervention arm using simple randomisation. Of the 13 matched pairs of neighbourhoods, one pair was excluded after 6 months due to too few pregnancies being reported (Figure 4.1).

4.3.3. Recruitment and participants

Pregnant women who were 18 years or older were identified by recruiters, local township women familiar with the neighbourhood's residents, who conducted house-to-house visits and obtained consent from eligible participants to be contacted again. The research team then obtained informed consent and recruited participants from an assessment centre situated locally. Recruitment took place between May 2009 and September 2010.

Due to slow recruitment, late-entry control participants were recruited in the consecutive assessments after giving birth (Rotheram-Borus *et al.*, 2011); these participants had no antenatal data and limited data on depressive symptom at follow-up assessments, and so were excluded from the analysis. Participants who gave birth to twins, died or whose baby died during the course of the study were also excluded (see Figure 4.1).

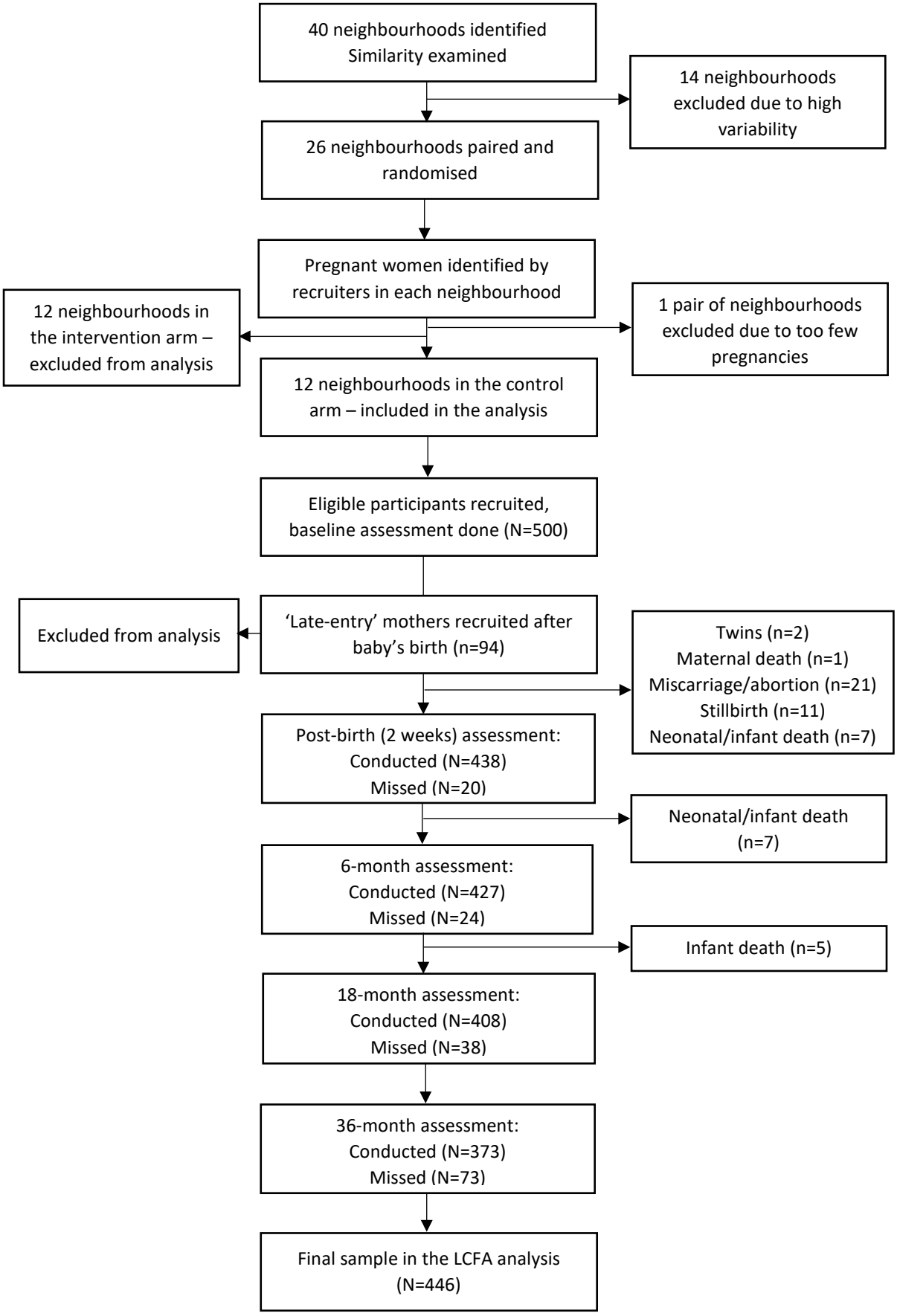

Figure 4.1 Recruitment and follow-up process

4.3.4. Measures

Assessments were translated and back translated into isiXhosa, as per standard guidelines (Brislin, 1986), and included a range of maternal and child measures (Rotheram-Borus *et al.*, 2011). These are briefly described below (also see Appendix H), and listed, by timepoint, in Table 4.1.

Demographic and obstetric characteristics (baseline only)

Self-reported demographic information collected at baseline included age, education, marital and employment status. Multiple correspondence analysis was employed to create a binary asset-based index of wealth (lower or higher wealth) to use as a proxy for socio-economic status at baseline (Booysen *et al.*, 2008), based on economic and asset-related measures. Self-reported obstetric measures, such as gestation at recruitment, gravidity, parity, whether the pregnancy was planned or wanted, and previous miscarriages were also collected, and so was HIV status.

Social characteristics (baseline only)

The number of friends and relatives the participants had, as well as the frequency of contact were recorded as a measure of social support at baseline. Whether the participant was living with the father of the baby was also recorded. Finally, participants reporting having been slapped, shoved, punched or threatened with a weapon by their partner in the past 12 months were classified as experiencing physical intimate partner violence (IPV).

Health characteristics

Depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS; (Cox *et al.*, 1987)), a 10-item Likert scale instrument assessing symptoms in the past week. Scores range from 0 to 30, with a greater score suggesting more severe depressive symptoms. This instrument has been validated among antenatal and postnatal women (Cox and Holden, 1994), and among isiXhosa-speaking women (Lawrie *et al.*, 1998, De Bruin *et al.*, 2004). Internal reliability of the EPDS was good at baseline (Cronbach's Alpha $\alpha = 0.88$).

Alcohol consumption during pregnancy (after discovery) was assessed using the Derived Alcohol Use Disorder Identification Test (AUDIT-C; (Dawson *et al.*, 2005)) – a three-item version of the original 10-item AUDIT (Saunders *et al.*, 1993). The last item related to the number of times three or more drinks were consumed in one sitting in the past month to reflect the definition of risky drinking for women in South Africa (Parry, 2001). Scores range from 0 to 12, and a score of three or more is indicative of risky drinking (Dawson *et al.*, 2005). The AUDIT-C correlates well with the AUDIT (Dawson *et al.*, 2005),

and has been used in previous research among Cape Town's township settlements (Kalichman *et al.*, 2008). Internal consistency at baseline was good (α = 0.86).

Table 4.1 Measures collected at each assessment

Measures	Assessment				
	1	2	3	4	5
Demographic characteristics	X				
Obstetric characteristics (including HIV status)	X				
Maternal social characteristics					
Social support (number of friends and frequency of contact)	X				
Intimate partner violence	X				
Maternal health characteristics					
Edinburgh Postnatal Depression Scale (EPDS)	X	X	X	X	X
Derived Alcohol Use Disorder Identification Test (AUDIT-C)	X	X	X	X	X
Child characteristics					
Anthropometric measures (length and weight)				X	X
Bayley Scales of Infant Toddler Development (motor and cognitive)				X	
Executive Functioning Battery					X
Child Behavioural Checklist					X
Strength and Difficulty Questionnaire					X

Note: 1=Baseline, 2=2-weeks postpartum, 3=6-months postpartum, 4=18-months postpartum, 5=36-months postpartum.

4.3.5. Child outcomes

Physical outcomes were assessed at 18 and 36 months postpartum, by measuring the infant's length and weight, using scales that were calibrated weekly. These were transformed into z-scores based on age- and gender-adjusted norms (WHO Multicentre Growth Reference Study Group, 2006).

The motor and cognitive subscales of the Bayley Scales of Infant Toddler Development (Bayley, 2003) were administered at 18 months to assess infants' cognitive and behavioural outcomes. Scaled scores, adjusted for age, were calculated for each subscale. Children's executive functioning, including working memory and attention shifting, was assessed at 36 months postpartum using the non-verbal Executive Functioning Battery (Blair *et al.*, 2016). This scale consists of three sections; Silly sounds (36 questions), Something's the same (28 questions) and Operation Span (16 questions). Scores for each section were generated by summing all correct responses.

Participants completed two instruments to assess children's socio-emotional and behavioural outcomes at 36 months: the Child Behaviour Checklist (CBCL; (Achenbach and Rescorla, 2000)) and the Strength and Difficulty Questionnaire (SDQ; (Goodman, 1997)). The CBCL is a 99-item three-point Likert scale questionnaire assessing children's externalising, internalising and inattention-

hyperactivity problems. The SDQ comprises 25 items measuring conduct and emotional symptoms, hyperactivity and peer relationships, all of which fall under 'total difficulties', as well as prosocial behaviour. The SDQ has been translated and used in a previous research in Cape Town among older children and adolescents (Cluver and Gardner, 2006).

4.3.6. Statistical analyses

Non-parametric tests were used to compare baseline socio-demographic, obstetric and health characteristics between participants who were included and excluded from the analyses, and between participants with and without data at 18 and 36 months postpartum (Chi Square and Mann-Whitney U tests, as appropriate). The analysis was then conducted in two steps – first a latent class growth analysis (LCGA), a type of GCMM, in Mplus version 8.0 (Muthén and Muthén, 1998-2015) and a series of multivariate analyses in Stata version 14 (StataCorp, 2015).

Identification of classes

With the use of LCGA, EPDS scores from baseline to 18 months postpartum were used to identify latent groups of individuals with similar growth curves (classes) over the extended postpartum period. To reflect the non-equidistant times between assessments, (Berlin *et al.*, 2014) factor loadings were set to 0 (baseline), 0.35 (2 weeks postpartum), 0.90 (6 months postpartum) and 2.10 (18 months postpartum). Participants completed on average 3.9 assessments (SD = 0.50) from baseline to 18 months postpartum. Missing data was assumed to be missing at random and was dealt with full information maximum likelihood estimation within Mplus. With this method, missing data was not imputed. Instead, it handles missing data directly in the model, whereby all non-missing data for each participant was taken into account to generate a maximum likelihood estimate of the missing data. A pseudo maximum likelihood approach (Huber-White sandwich estimator (Froot, 1989)) was implemented to adjust the estimates' standard errors for clustering by neighbourhood.

In a preliminary single-class analysis, the quadratic function fit the data significantly better that a linear one (Hu and Bentler, 1999). A quadratic polynomial growth function was thus chosen to allow for non-linear trajectories in all subsequent models. The optimal number of classes for the final model was chosen by comparing models with different number of classes according to the Bayesian and Akaike Information Criteria (Akaike, 1983, Raftery, 1995), the entropy (Ramaswamy *et al.*, 1993) and the average probability of class membership (posterior probability). The Lo-Mendel-Rubin test (LMRT) (Lo *et al.*, 2001) and Bootstrap Likelihood Ratio Test (BLRT) (McLachlan and Peel, 2004) were also used to test the difference in fit between successive models. Finally, the size and theoretical interpretability

of classes were also considered. After fitting the final model, participants were assigned to latent classes based on their highest posterior probability.

Predictors and outcomes of trajectories

To identify predictors of trajectories generated through the LCGA, a series of univariate unadjusted multinomial logistic regressions were conducted, with class membership as outcome, and baseline socio-demographic, obstetric and health characteristics as predictors. Class membership was then entered as a predictor in linear and logistic regressions to assess continuous and binary child outcomes, respectively, at 18 and 36 months. Each of these models were adjusted for age, education and wealth status, factors shown to be confounders in the relationship between maternal depression and child outcomes (Rahman *et al.*, 2004, Rowe and Goldin-Meadow, 2009, Grote *et al.*, 2010, Parsons *et al.*, 2012). To avoid reporting bias due to concurrent depressive symptoms, known to affect maternal reports of child behaviour (Goodman *et al.*, 2011, Müller *et al.*, 2011), models assessing maternal reports of child outcomes at 36 months were adjusted for participants' EPDS score. This was not necessary for child outcomes at 18 months, however, since the EPDS was used to generate the latent trajectories of depressive symptoms.

4.3.7. Ethics

The cluster RCT was approved by the Institutional Review Boards of the University of California Los Angeles (G07-02-022) and Stellenbosch University Institutional Review Board (N08/08/218) (Appendix I). This study was approved by the University of Cape Town (HREC REF 835/2015).

4.4. Results

A total of 594 pregnant women were recruited from 12 control arm neighbourhoods, each comprising 20 to 60 participants. After excluding late-entry participants (n = 94), and participants who gave birth to twins (n = 2), who died or whose baby died during the study (from baseline to 18 months postpartum; n = 52), the final sample was 446 (Online Resource 1). Sensitivity analyses showed that physical, cognitive, socio-emotional and behavioural outcomes at 18 and 36 months did not differ significantly between participants recruited during pregnancy and late-entry participants, besides weight-for-length and weight-for-age z-scores at 36 months. Thus, sampling bias was not introduced by excluding the late-entry participants from the analysis. However, participants recruited at baseline and excluded from the analyses were recruited earlier in pregnancy (Median, Mdn = 17.5 weeks, Interquartile range, IQR = 13-26) and reported higher EPDS scores at baseline (Mdn = 13, IQR = 7-19),

compared to those included (gestation: Mdn = 27.5 weeks, IQR = 21-34, p < 0.001; EPDS: Mdn = 10, IQR = 5-16, p = 0.011).

Baseline characteristics of the final sample are presented in Table 4.2. Participants had a mean age of 26 years (Standard deviation, SD = 5.30), and were recruited, on average, at 26.6 weeks gestation (SD = 8.03), corresponding to the sixth month of gestation. Only a minority reported completing high school (n = 110, 24.7%), working (n = 83, 18.6%) and not having a partner (n = 27, 6.1%). Over a third (n = 174, 39.0%) reported having experienced IPV in the previous year and 26.2% (n = 107) reported being HIV-positive at baseline.

Compared to participants who were followed-up, participants lost to follow-up (n = 38, 8.5%) reported lower baseline EPDS scores (Mdn = 6, IQR = 2-12 vs. Mdn = 10, IQR = 5-16, $U = 2.79$, $p = 0.005$) and the majority were from the lower wealth category (n = 26, 68.4% vs. n = 197, 48.3%, $\chi^2 = 5.64$, $p = 0.026$). At 36 months postpartum, a greater proportion of participants lost to follow-up (n = 73, 16.4%) were from the lower wealth category (n = 46, 63.0 vs. n = 177, 47.5%, $\chi^2 = 5.91$, $p = 0.021$), and a smaller proportion reported experiencing IPV (n = 21, 28.8% vs n = 153, 41.0%, $\chi^2 = 3.85$, $p = 0.050$).

Table 4.2 Characteristics of participants at baseline, and across allocated trajectory

Variable	Total (N = 446)		Chronic low (N = 317)		Late postpartum (N = 45)		Early postpartum (N = 64)		Chronic high (N = 20)	
	n	%	n	%	n	%	n	%	n	%
Socio-demographic characteristics										
Age (mean, SD)	26.0	5.30	26.0	5.23	26.7	5.69	25.2	5.31	27.1	5.58
Did not complete high school	336	75.3	232	73.2	32	71.1	54	84.4	18	90.0
No current partner	27	6.1	17	5.4	1	2.2	7	10.9	2	10.0
Currently unemployment	363	81.4	246	77.6	35	77.8	62	96.9	20	100.0
Lower wealth	223	50.0	160	50.5	21	46.7	32	50.0	10	50.0
Not Living with father of child	209	46.9	148	46.7	22	48.9	30	46.9	9	45.0
Experienced IPV in past year	174	39.0	112	35.3	23	51.1	30	46.9	9	45.0
Low social support (score ≤ median) [a]	227	50.9	148	46.7	27	60.0	37	57.8	15	75.0
Obstetric characteristics										
Gestation (in weeks) (mean, SD)	26.6	8.03	26.6	8.02	26.1	8.66	27.0	7.31	23.9	8.38
Primigravida	155	34.8	107	33.8	19	42.2	24	37.5	5	25.0
Primipara	173	38.8	119	37.5	21	46.7	28	43.8	5	25.0
Unplanned pregnancy	322	72.4	224	70.9	37	82.2	46	71.9	15	75.0
Unwanted pregnancy	25	5.6	14	4.4	2	4.4	6	9.4	3	15.0
Previous miscarriage (n=328)	18	6.2	12	5.7	2	7.7	4	10.0	0	0
Health characteristics										
EPDS score (mean, SD)	10.9	6.86	9.9	6.54	12.2	6.51	13.1	7.50	15.7	6.96
Risky drinking [b]	20	4.5	14	4.4	1	2.2	2	3.2	3	15.0
HIV positive status (n=411)	107	26.2	65	22.3	13	32.5	22	37.9	7	36.8

[a] calculated as number of friends/relatives multiplied by frequency of contact; [b] defined as a score of 3 or more on AUDIT-C

4.4.1. Trajectories

The LCGA indices led to a 4-class model (Table 4.3), which had the highest entropy (0.963) and fit significantly better than a 3-classes model, according to the LMRT and BLRT values (Table 4.3). The smallest class included 4.5% of the sample (n = 20). The change in mean EPDS scores over time among women in each of the 4 classes (Figure 4.2) suggests a combination of chronic and transient symptom trajectories: 1) *chronic low* trajectory (n = 317, 71.1%), with a highest mean EPDS score at baseline (mean = 9.9, SD = 6.54), which steadily decreases; 2) *late postpartum* trajectory (n = 45, 10.1%), with a slightly higher baseline mean score which increases sharply to 22.1 (SD = 1.95) at 18 months postpartum; 3) *early postpartum* trajectory (n = 65, 14.4%), with a mean baseline scores just above the severity cut-off of 13 (Rochat *et al.*, 2013b), which reaches a maximum mean score of 22.3 (SD = 3.6) at 6 months postpartum and declines to very low levels at 18 months postpartum; and 4) *chronic high* trajectory (n = 20, 4.5%), with a mean baseline score of 15.7 (SD = 6.96), which increases steadily to 22.5 (SD = 3.79) at 6 months and stabilises.

Table 4.3 Latent class growth analysis: comparisons of models with different number of classes

Classes	AIC	BIC	Entropy	Size (%) of smallest class	LMRT statistic (p-value)	BLRT statistic (p-value)
2	11155.037	11200.140	0.955	15.0	559.562 (<0.001)	-5857.765 (<0.001)
3	10956.411	11017.916	0.951	14.1	198.491 (0.012)	-5566.518 (0.011)
4	**10735.106**	**10813.012**	**0.963**	**4.5**	**220.278 (<0.001)**	**-5463.206 (<0.001)**
5	10686.188	10780.495	0.851	4.2	54.677 (0.531)	-5348.553 (0.517)
6	10634.828	10745.536	0.875	3.8	57.023 (0.188)	-5320.094 (0.180)
7	10618.594	10745.704	0.866	3.8	23.280 (0.553)	-5290.414 (0.546)

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; BLRT=Bootstrap Likelihood Ratio Test; LMRT=Lo-Mendell-Rubin Test.

4.4.2. Predictors

The results of the univariate multinomial logistic regressions to assess baseline predictors of trajectories are presented in Table 4.4. The *chronic low* trajectory was used as the reference category. The risk of belonging to the *chronic high* trajectory, versus the *chronic low* trajectory, among those who reported below average social support, an unwanted pregnancy and risky drinking was 3.43 (95%CI 1.22, 9.65), 3.82 (95%CI 1.00, 14.57) and 3.82 (95%CI 1.00, 14.57) times as high, respectively, as the risk of belonging to this trajectory when these characteristics were not reported. The risk of belonging to the *early postpartum* trajectory among those who were unemployed and those who were HIV-positive was 8.95 (95%CI 2.14, 37.48) and 2.13 (95%CI 1.17, 3.88) times as high as the risk of

belonging to this trajectory when participants reported being employed and HIV negative, respectively. The risk of belonging to the *late postpartum* trajectory among those who reported IPV in the year preceding recruitment was 1.91 (95%CI 1.02, 3.59) times as high as the risk of belonging to this trajectory when no IPV was reported.

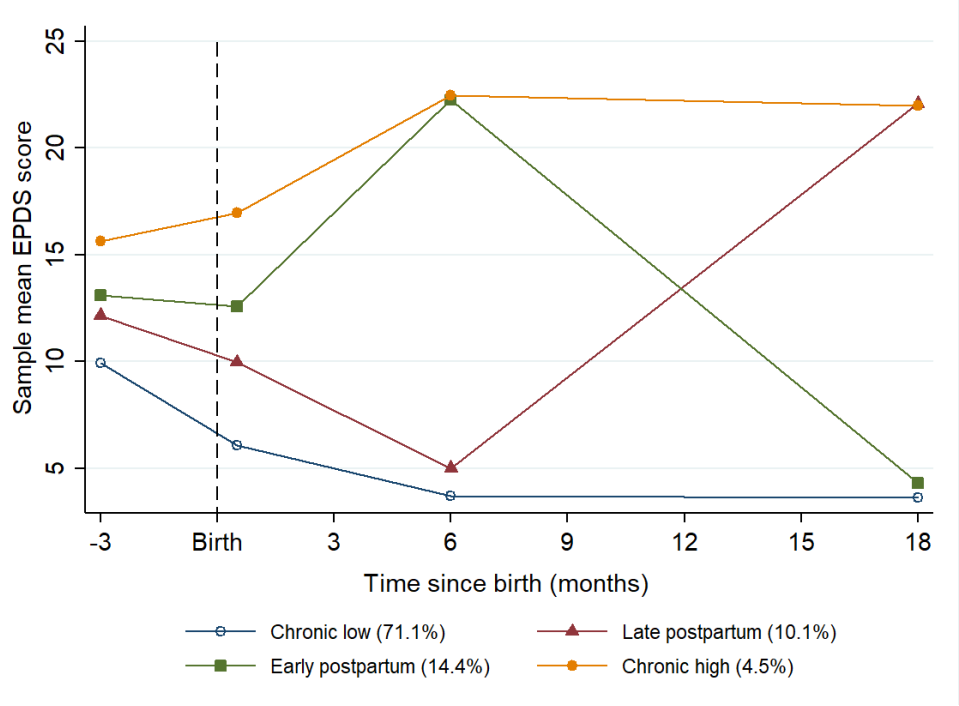

Figure 4.2 Sample mean EPDS curves of the LCGA 4-class solution

4.4.3. Child outcomes

The results of the linear and logistic regressions assessing child outcomes at 18 and 36 months in relation to the trajectories, adjusted for age, education and wealth, are presented in Table 4.5. Again, the *chronic low* trajectory was used as the reference trajectory.

18 months outcomes

Children of participants allocated to the *late postpartum* trajectory had significantly lower weight-to-length (mean = 0.11, SD = 1.36) and weight-for-age z-scores (mean = -0.22, SD = 1.09) compared to children of participants in the *chronic low* trajectory (weight-to-length z-score: mean = 0.91, SD = 1.33; adjusted β (aβ) = -0.81; 95%CI -1.27, -0.34; weight-for-age z-scores: mean = 0.41, SD = 1.22, aβ = -0.63; 95%CI -1.05, -0.21). The same pattern could be seen among children of participants allocated to the *early postpartum* trajectory, with children reporting lower weight-to-length (mean = 0.36, SD = 1.33, aβ = -0.52; 95%CI -0.92, -0.11) and weight-to-age z-scores (mean = -0.09, SD = 1.23; aβ = -0.45; 95%CI -0.81, -0.09) compared to children of participants in the *chronic low* trajectory.

Table 4.4 Baseline predictors of classes identified through the latent class growth analysis, in comparison to the chronic low *trajectory*

	Late postpartum (N = 45)			Early postpartum (N = 64)			Chronic high (N = 20)		
Variable	RRR	95%CI	*p*	RRR	95% CI	*p*	RRR	95%CI	*p*
Socio-demographics characteristics									
Age	1.03	0.97 to 1.09	0.389	0.97	0.92 to 1.02	0.274	1.04	0.96 to 1.13	0.374
Did not complete high school	0.90	0.45 to 1.80	0.769	1.98	0.96 to 4.06	0.063	3.30	0.75 to 14.51	0.115
Currently unemployed	1.01	0.48 to 2.14	0.979	8.95	2.14 to 37.48	0.003	-	-	-
Lower wealth	1.08	0.79 to 1.48	0.633	1.01	0.77 to 1.32	0.945	1.01	0.64 to 1.59	0.967
No partner	0.40	0.05 to 3.08	0.379	2.16	0.86 to 5.44	0.103	1.95	0.42 to 9.12	0.394
Not living with father of child	1.09	0.58 to 2.04	0.782	1.01	0.59 to 1.73	0.978	0.93	0.38 to 2.32	0.883
Lower social support (score ≤ median) [a]	1.71	0.91 to 3.24	0.097	1.56	0.91 to 2.69	0.106	3.43	1.22 to 9.65	0.020
Experienced IPV in past year	1.91	1.02 to 3.59	0.043	1.62	0.94 to 2.78	0.083	1.50	0.60 to 3.72	0.385
Obstetric characteristics									
Primigravida	1.43	0.76 to 2.71	0.266	1.18	0.67 to 2.06	0.565	0.65	0.23 to 1.85	0.423
Primipara	1.46	0.78 to 2.73	0.241	1.29	0.75 to 2.23	0.353	0.55	0.20 to 1.56	0.265
Unplanned pregnancy	1.90	0.85 to 4.24	0.117	1.05	0.58 to 1.91	0.874	1.23	0.44 to 3.49	0.694
Unwanted pregnancy	1.01	0.22 to 4.58	0.993	2.24	0.83 to 6.07	0.113	3.82	1.00 to 14.57	0.050
Health characteristics									
Risky drinking [b]	0.49	0.06 to 3.83	0.498	0.71	0.16 to 3.20	0.655	3.82	1.00 to 14.57	0.050
HIV positive	1.68	0.82 to 3.44	0.155	2.13	1.17 to 3.88	0.013	2.04	0.77 to 5.39	0.151

[a] Calculated as number of friends/relatives multiplied by frequency of contact; [b] defined as a score of 3 or more on AUDIT-C; RRR=Relative risk ratios; CI=confidence intervals.

36 months outcomes

Results indicate that children of participants in the *late postpartum* trajectory had lower weight-for-age z-scores (mean = -0.20, SD = 0.99) compared to children of participants allocated to the *chronic low* trajectory (mean = 0.23, SD = 1.09; aβ = -0.43; 95%CI -0.78, -0.07). Children of participants in the *early postpartum* trajectory reported significantly lower length-for-age (mean = -1.83, SD = 1.07, aβ = -0.55; 95%CI -0.90, -0.21) and weight-for-age z-scores (mean = -0.34, SD = 0.94; aβ = -0.54; 95%CI -0.87, -0.21).

Scores on the Executive Functioning Battery did not differ across trajectories. There were also no differences in internalising, externalising or total problem scores on the CBCL, nor differences in total difficulty score on the SDQ. However, children of participants in the *chronic high* trajectory reported greater emotional symptom scores (mean = 2.2, SD = 2.66), and children of participants in the *late postpartum* trajectory had greater peer problem scores (mean = 3.0, SD = 1.26), compared to children in the *chronic low* trajectory (emotional: mean = 1.1, SD = 1.47, aβ = 0.96; 95%CI 0.17, 1.75; peer problems: mean = 2.6, SD = 1.13, aβ = 0.42 95%CI 0.0.02, 0.81). Finally, children of participants in the *early postpartum* trajectory (mean = 8.2, SD = 1.62; aβ = 0.85; 95%CI 0.21, 1.50) and in the *chronic high* trajectory (mean = 8.5, SD = 1.5; aβ = 1.19; 95%CI 0.14, 2.24) reported greater SDQ prosocial scores compared to children of participants in the *chronic low* trajectory (mean = 7.5, SD = 2.22).

4.5. Discussion

This study sought to identify latent trajectories of depressive symptoms from pregnancy to 18 months postpartum, and their predictors, among low-income perinatal women in South Africa. Altogether, the four trajectories identified support previous findings using similar modelling techniques (Baron *et al.*, 2017, Santos *et al.*, 2017). First, the *chronic low* trajectory identified was reported in one previous study conducted in Africa (Barthel *et al.*, 2017), suggesting that, despite the high number and ongoing stressors experienced in LMICs, the majority of women remain at low risk for developing depressive symptoms during the perinatal period. Second, the *early postpartum* and *late postpartum* trajectories identified are also similar to those reported by Barthel et al (Barthel *et al.*, 2017). In their study conducted among perinatal women in Ghana and Côte d'Ivoire, they report that besides family and financial stress, none of the sociodemographic or psychosocial factors were associated with these trajectories. Findings were similar in our study: only IPV in the year leading to pregnancy was identified as a risk factor for *late postpartum* depressive symptoms, and unemployment and HIV-positive status as risk factors for *early postpartum* depressive symptoms. The latter finding corroborates past research in South Africa indicating that being diagnosed with HIV during pregnancy can put mothers

Table 4.5 Child outcomes at 18 and 36 months postpartum across classes identified through latent class growth analysis

	Chronic low (N = 239)	Late postpartum (N = 37)			Early postpartum (N = 54)			Chronic high (N = 16)		
	Mean (SD)	Mean (SD)	Adjusted β (95%CI)	*p*	Mean (SD)	Adjusted β (95%CI)	*p*	Mean (SD)	Adjusted β (95%CI)	*p*
18-MONTH OUTCOMES										
Physical outcomes [a]										
Length-for-age z-score	-0.55 (1.17)	-0.65 (0.99)	-0.08 (-0.47 to 0.30)	0.666	-0.68 (1.05)	-0.10 (-0.43 to 0.23)	0.566	-0.72 (0.87)	-0.09 (-0.65 to 0.48)	0.761
Weight-to-length z-score	0.91 (1.33)	0.11 (1.36)	-0.81 (-1.27 to -0.34)	0.001	0.36 (1.33)	-0.52 (-0.92 to -0.11)	0.012	0.50 (1.50)	-0.40 (-1.08 to 0.29)	0.253
Weight-for-age z-score	0.41 (1.22)	-0.22 (1.09)	-0.63 (-1.05 to -0.21)	0.003	-0.09 (1.23)	-0.45 (-0.81 to -0.09)	0.014	0.03 (1.37)	-0.33 (-0.94 to 0.29)	0.297
Motor and cognitive outcomes (Bayley) [a, b]										
Cognitive scaled score	10.14 (3.03)	9.59 (3.30)	-0.53 (-1.89 to 0.84)	0.445	10.24 (2.72)	0.08 (-1.32 to 1.49)	0.905	9.00 (1.84)	-1.10 (-2.96 to 0.77)	0.247
Gross motor scaled score	10.99 (2.88)	10.64 (3.58)	-0.47 (-1.80 to 0.86)	0.488	10.57 (3.06)	-0.45 (-1.82 to 0.92)	0.514	10.82 (1.47)	-0.24 (-2.06 to 1.57)	0.792
Fine motor scaled score	10.01 (1.90)	9.55 (2.65)	-0.50 (-1.40 to 0.39)	0.273	10.81 (1.50)	0.87 (-0.06 to 1.79)	0.067	9.27 (2.15)	-0.76 (-1.99 to 0.46)	0.221
36-MONTH OUTCOMES										
Physical outcomes [a]										
Length-for-age z-score	-1.24 (1.13)	-1.59 (1.03)	-0.35 (-0.72 to 0.02)	0.064	-1.83 (1.07)	-0.55 (-0.90 to -0.21)	0.002	-1.35 (1.44)	-0.06 (-0.61 to 0.48)	0.818
Weight-to-length z-score	1.33 (1.19)	1.00 (1.33)	-0.34 (-0.74 to 0.07)	0.108	1.00 (1.26)	-0.32 (-0.70 to 0.06)	0.096	1.11 (1.08)	-0.21 (-0.81 to 0.39)	0.492
Weight-for-age z-score	0.23 (1.09)	-0.20 (0.99)	-0.43 (-0.78 to -0.07)	0.018	-0.34 (0.94)	-0.54 (-0.87 to -0.21)	0.001	0.01 (1.03)	-0.19 (-0.71 to 0.34)	0.486
Socio-emotional and behavioural outcomes [c]										
CBCL total problem score	11.0 (21.44)	48.5 (21.09)	2.94 (-4.30 to 10.19)	0.425	45.9 (27.14)	-0.24 (-6.96 to 6.48)	0.944	52.3 (30.94)	4.38 (-6.61 to 15.38)	0.433
Internalising score	12.2 (7.82)	14.8 (7.71)	2.10 (-0.50 to 4.69)	0.112	13.7 (9.31)	0.85 (-1.53 to 3.22)	0.484	15.1 (10.73)	1.80 (-2.07 to 5.57)	0.362
Externalising score	16.7 (8.74)	16.7 (9.00)	-0.47 (-3.39 to 2.46)	0.753	15.8 (10.73)	-1.67 (-4.35 to 1.01)	0.220	17.4 (10.67)	-0.32 (-4.69 to 4.04)	0.885
SDQ total difficulty score	9.2 (4.33)	9.9 (4.75)	0.47 (-1.02 to 1.96)	0.535	9.9 (4.98)	0.25 (-1.13 to 1.63)	0.721	10.8 (6.69)	0.89 (-1.37 to 3.15)	0.438
Emotional symptom score	1.1 (1.47)	1.5 (1.81)	0.39 (-0.13 to 0.91)	0.145	1.2 (1.71)	0.05 (-0.43 to 0.53)	0.835	2.2 (2.66)	0.96 (0.17 to 1.75)	0.018
Conduct problem score	2.4 (2.23)	2.0 (2.25)	-0.46 (-1.20 to 0.28)	0.221	2.7 (2.41)	0.16 (-0.53 to 0.85)	0.646	2.1 (2.19)	-0.46 (-1.59 to 0.66)	0.417
Hyperactivity score	3.2 (1.49)	3.4 (1.59)	0.13 (-0.37 to 0.63)	0.615	3.3 (1.61)	-0.07 (-0.53 to 0.40)	0.777	3.5 (1.84)	0.12 (-0.64 to 0.88)	0.752
Peer problem score	2.6 (1.13)	3.0 (1.26)	0.42 (0.02 to 0.81)	0.039	2.8 (1.41)	0.11 (-0.26 to 0.47)	0.572	2.9 (1.39)	0.27 (-0.32 to 0.88)	0.364
SDQ prosocial score	7.5 (2.22)	7.2 (2.15)	-0.21 (-0.90 to 0.48)	0.553	8.2 (1.62)	0.85 (0.21 to 1.50)	0.009	8.5 (1.50)	1.19 (0.14 to 2.24)	0.027
Cognitive outcomes (EFB) [a]										
Silly Sounds score	5.7 (7.54)	5.5 (7.84)	-0.28 (-2.87 to 2.31)	0.833	5.0 (8.73)	-0.75 (-3.17 to 1.66)	0.539	3.9 (5.85)	-1.77 (-5.59 to 2.06)	0.364
Operating Span score	1.4 (2.56)	1.3 (2.03)	-0.10 (-0.95 to 0.75)	0.813	1.1 (1.93)	-0.29 (-1.08 to 0.50)	0.473	2.3 (4.18)	0.84 (-0.42 to 2.10)	0.189
Something's The Same score	3.6 (4.62)	3.6 (4.81)	-0.04 (-1.64 to 1.56)	0.961	3.5 (5.28)	-0.11 (-1.59 to 1.38)	0.885	3.5 (4.74)	-0.14 (-2.49 to 2.21)	0.905

[a] All outcomes adjusted for age, education and wealth; [b] Sample size 197 (Cognitive and fine motor scaled score) and 196 (Gross motor scaled score); [c] adjusted for age, wealth, education and EPDS scores at 36 months; CBCL=Child Behaviour Checklist; EFB=Executive Functioning Battery; SD=Standard deviation; SDQ=Strength and Difficulty Questionnaire. NOTE: greater scores on CBCL subscales and SDQ total difficulty subscales suggest greater symptom severity, while lower scores on SDQ prosocial subscale suggest greater symptom severity.

at increased risk of postnatal depression (Rochat *et al.*, 2006). The practical implications of inadequate resources to provide for a new baby, once the baby is born, could also explain the association found between unemployment and the *early postpartum* trajectory (Lee *et al.*, 2007). Finally, women with chronically severe symptoms, reported in previous research in South Africa (Chapter 3), seem to be a high-risk group, as they reported having less social support, were more likely to report an unwanted pregnancy and more likely to have been engaging in risky drinking behaviour during pregnancy. Likewise, the high-risk *antenatal and postnatal* trajectory in Chapter 3's study was associated with lower social support and heavy drinking during pregnancy.

The fact that two of the four trajectories identified have transient patterns indicate that a single screening for depressive symptoms may not be enough to identify women at risk for perinatal depression. Instead, repeated screening conducted throughout pregnancy and the first year postpartum would be more effective, perhaps in the context of antenatal and well-baby visits. Alternatively, and as our findings suggest, screening for other factors, such as lack of social support, alcohol use and IPV, in antenatal settings may be a way of identifying pregnant women who may be at risk for chronic symptoms or of worse symptoms later in the postpartum period.

The second aim of our study was to investigate the association between trajectories of perinatal depression symptoms and child outcomes at 18 and 36 months postpartum. Important distinctions were found in children's physical outcomes across trajectories, and this even after controlling for known demographic confounders, including wealth, suggesting that poorer physical outcomes were not solely due to children's social or economic environment. Also, the fact that weight-to-length z-scores, a short-term response to inappropriate nutrition (Parsons *et al.*, 2012), and length-for-age z-scores, a longer-term cumulative response to poor diet and recurrent illness (Parsons *et al.*, 2012), were lower at 18 and 36 months, respectively, among children of mothers in the *early postpartum* trajectory suggest that the effect of postnatal depressive symptoms may have long-lasting effects on child physical outcomes. Emerging evidence suggests that psychosocial interventions for depression which include parenting or caregiving components are the most effective in improving both maternal mental health and child outcomes (Parsons *et al.*, 2012). Given the impact of depressive symptoms on children's physical outcomes in this study, it may be worth including a nutritional advice component in psychosocial interventions addressing perinatal depressive symptoms.

Surprisingly, the motor or cognitive outcomes of infants at 18 months, and executive functioning at 36 months, thought to be an indicator of learning disability even when cognitive abilities seem intact (Riggs *et al.*, 2004), did not differ across depressive symptom trajectories. There were also no

differences in overall socio-emotional or behavioural outcomes on the SDQ or CBCL questionnaires at 36 months postpartum. However, the investigation of the SDQ subscales indicated that children of mothers with chronically severe symptoms had greater emotional symptom problems, and children of mothers among the *late postpartum* trajectory had greater peer-related problems, compared to children of mothers with low depressive symptoms. This corroborates Vänskä et al. (2011)'s study, where no differences in externalising symptoms could be found across different trajectories of depression, but children of mothers with chronically severe symptoms showed greater internalising symptoms compared to children of mothers with stable low symptoms.

As suggested by Prenoveau et al (Prenoveau *et al.*, 2017), it may be that mothers' low positive affect is more detrimental to children' emotional negativity specifically. However, previous studies using similar modelling techniques did find that children of mothers with chronic or transient depressive symptoms reported poorer executive functioning and greater emotional and behavioural problems (Vänskä *et al.*, 2011, Giallo *et al.*, 2015b, van der Waerden *et al.*, 2015). These studies were conducted in HICs, however, and the impact of depressive symptoms on children's development may differ in LMICs, where social and psychological factors, such as poverty and cultural norms, are likely to play an important role. It was beyond the scope of this study to investigate moderating or mediating factors of child development; however future research in LMICs should to further our understanding of the underlying mechanisms between maternal depression and child development.

Differences in child outcomes across trajectories may also have been detected had analyses been stratified by gender. Indeed, preliminary analyses indicated that, overall, girls reported lower scores on the internalising and externalising subscales of the CBCL. However, the small sample size in the *early postpartum*, *late postpartum* and *chronic high* trajectories meant that it was not possible to report child outcomes across trajectories and gender. There is, however, growing evidence that there may be gender differences in the way maternal mental disorders impact on their children (Goodman *et al.*, 2011, Sohr-Preston and Scaramella, 2006). Thus, it is imperative that future studies address this gap, as this could have important implications on our understanding of chronicity and severity of perinatal depressive symptoms on child development.

4.5.1. Limitations

Several limitations should be noted. First, a potentially high-risk group of mothers may have been excluded from the analysis by excluding those whose babies died during the course of the study. This is supported by the fact that these women reported greater depressive symptoms at baseline

compared to women included in our study. Given that our main objective was to assess trajectories of depressive symptoms in relation to child outcomes, this was a necessary exclusion criterion. However, this limitation should be borne in mind when interpreting and comparing the trajectories identified here with those reported in previous studies using similar analytical approaches.

Second, while LCGA overcomes some of past research's pitfalls, assessments were still limited and wide apart. Our interpretation of 'chronic' symptoms therefore remains simplistic. With only one assessment conducted during pregnancy, we cannot assess whether symptoms fluctuated during pregnancy, or whether they were a continuation of pre-pregnancy symptoms. Also, the second assessment was conducted within the first two weeks postpartum, so depressive symptoms may have reflected baby blues, rather than postnatal depression per se. Moreover, the EPDS is a valid measure of depressive symptoms during the perinatal period, but the exclusion of somatic symptoms means it may not be valid at 18 or 36 months postpartum. The potential underestimation of depressive symptom severity at these assessments may have affected the 18-month mark of trajectories identified through LCGA. It may also have led to underestimate the effect of depressive symptoms on mothers' reports of child development at 36 months, which was controlled for in the analysis. This may partly explain the lack of association between depressive symptoms trajectories and behavioural outcomes.

A further limitation relating to the use of LCGA is that it assumes no intra-class variance in the growth parameters, which may have been too restrictive. However, allowing free variance for the intercepts produced a negligible improvement in fit and no substantive changes in the shape of the trajectories or in the overall distribution of the sample across classes. Models also did not converge when free variance was allowed for the slope and quadratic terms (i.e. moving from LCGA to growth mixture modelling). While this could be due to an insufficient sample size, this may reflect the absence of significant variability, suggesting that LCGA may be an appropriate method to model our data nonetheless.

The little intra-class variability also supports the 4-class model identified, despite the small sample size of the chronic-high trajectory. However, a small sample size meant that we may not have had enough power to identify meaningful differences between trajectories, especially between the *chronic high* and low trajectories. A small sample size also meant that univariate, rather than multivariate, analyses of risk factors were more appropriate. However, though not reported here, the patterns of risk for each trajectory did not change substantially when multivariate analyses of risk factors were conducted, despite the presence of broad confidence intervals.

Finally, all analyses conducted in Stata to assess predictors and child outcomes considered class membership as observed, rather than predicted by the LCGA model. However, given the high classification accuracy showed by our 4-class model, it is unlikely that taking into account this uncertainty in regression models would have produced substantive changes in the interpretation of the results.

4.6. Conclusions

To our knowledge, this is the first study in Sub-Saharan Africa to have used GCMM to assess the course of perinatal depressive symptoms in relation to child development. Despite several limitations, our study has clear implications for the identification of at-risk populations and for the development of preventive interventions to promote maternal mental health and child development. Mothers remain at risk for developing severe symptoms after one year postpartum, and while several psychosocial factors can help identify pregnant women likely to suffer from chronic or late postpartum depression, policy makers and practitioners must recognise the need for multiple screening assessments throughout pregnancy and the first year postpartum.

Our study does not support the idea that there are sensitive periods in which maternal depressive symptoms have qualitatively different impact on children's development. Instead, it seems the presence of depressive symptoms at any point during the perinatal period can have adverse effects on children's physical and socio-emotional outcomes. Further investigation in LMICs is warranted, with bigger samples and more frequent assessments. This will help tease out the relative importance of chronicity of symptoms versus severity, identify whether antenatal and postnatal depressive symptoms have independent or interactive effects on child outcomes, and work towards identifying pathways between perinatal depression and child outcomes that are specific to LMICs.

Chapter 5. Longitudinal association between perinatal depressive symptoms and suicidal risk

5.1. Brief overview

The aim of the study in this Chapter was to assess the association between depressive symptoms and suicidal risk over time among perinatal women at risk for antenatal depression, and assess modifying effects of age, perinatal stage and depressive symptom trajectory. A total of 384 adult pregnant women were recruited from two antenatal clinics in a township settlement near Cape Town, South Africa, and followed-up at eight months gestation, and at three and 12 months postpartum. The MINI 6.0 Suicidality module and the Hamilton Depression Rating Scale (HDRS) were used to measure suicidal risk and depression, respectively. Generalised Estimating Equations were used to assess the association between change in depressive symptoms from one assessment to the next (predictor) and change in suicide score or change in suicidal risk (score ≥ 9) (outcomes). A one-point unit change in HDRS score was associated with a 0.57-point unit change in suicide score (95%CI 0.35, 0.78; $p < 0.001$). After controlling for risk of suicide at the previous assessment, a one-point unit change in HDRS score was also associated with a one-point and with greater odds of being at moderate risk for suicide (adjusted odds ratio = 1.15; 95%CI 1.09, 1.22; $p < 0.001$). Age was a significant effect modifier: change in HDRS scores was not associated with change in suicide scores among participants aged 35-45 years. Secondary analyses indicated that a one-unit decrease in HDRS score was associated with a decrease in suicide scores, but a one-unit increase in HDRS score was not associated with change in suicide score. Results suggest that depression and suicide are overlapping but relatively independent phenomena, especially among older or more chronically depressed perinatal women.

5.2. Introduction

Suicide was recently estimated the 18th leading cause of death globally (World Health Organization, 2018a). Contrary to high-income countries (HIC), where the risk of suicide increases with age (Bachmann, 2018), suicide in low- and middle-income countries (LMICs) is the leading cause of death among 15 to 29-year olds (World Health Organization, 2018a). It is also the leading cause among women aged 15-19 years (Petroni *et al.*, 2015), ahead of maternal mortality. In South Africa, 1% of maternal deaths were due to suicide between 2014 and 2016 (National Committee for Confidential

Enquiries into Maternal Deaths, 2018), while the prevalence of suicidal ideation ranges between 14% and 28% among perinatal women (Lindahl *et al.*, 2005, Rochat *et al.*, 2013a, Onah *et al.*, 2017).

Globally, rates of suicide are usually lower among the perinatal population compared to the general population (Lindahl *et al.*, 2005), thought to be because women who get pregnant are usually healthier (Ronsmans *et al.*, 2000), or because of women's concern for the foetus and increased social support and contact with health services during pregnancy (Lindahl *et al.*, 2005). This may be less applicable in LMICs, however, where pregnancies are more likely to occur in the context of HIV, poverty, substance use, interpersonal violence and lack of partner support (Rochat *et al.*, 2006, Jewkes *et al.*, 2010, Schwartz *et al.*, 2012, Tomlinson *et al.*, 2013) – all of which have been shown to increase the risk of suicide in LMICs (Mars *et al.*, 2014, Bantjes *et al.*, 2016, Bachmann, 2018) and South Africa more specifically (Dewing *et al.*, 2013, Rochat *et al.*, 2013a). These have also been identified as risk factors for perinatal depression, which is estimated to affect 13% of women in LMICs (Woody *et al.*, 2017). In South Africa, the prevalence of antenatal and postnatal depression recorded has been as high as 47% and 35%, respectively (Cooper *et al.*, 1999, Rochat, 2011).

Unsurprisingly, depression and suicidal behaviours (ideation, plan or attempt) are strongly associated. Globally, approximately 90% of individuals who commit suicide suffer from a mental disorder (Arsenault-Lapierre *et al.*, 2004), and half of these suffer from depression or a mood disorder (Holma *et al.*, 2014, Bachmann, 2018). In South Africa, results from the South African Stress and Health (SASH) study, a 2002 survey among a representative sample of South African adults, indicated that 24% and 27% of individual reporting lifetime suicidal ideation and attempts, respectively, had a history of major depression (Khasakhala *et al.*, 2011). Similar associations between depression and suicidal ideation have been reported among perinatal women in South Africa (Dewing *et al.*, 2013, Rochat *et al.*, 2013a, Onah *et al.*, 2017). However, Onah *et al.* (2017) found that a diagnosis of mood disorder among pregnant women, whilst associated with suicidal ideation, was not associated with suicide plan or attempt. Also, in the same study, more than half of women who reported suicidal behaviour did not suffer from depression, anxiety or personality disorder. This mirrors findings reported among the general population in South Africa (Khasakhala *et al.*, 2011) and other LMICs (Nock *et al.*, 2009), suggesting that depression and suicidal risk may be overlapping but separate entities (Lindahl *et al.*, 2005).

Latent modelling techniques have shown that trajectories of perinatal depressive symptoms are heterogenous (Baron *et al.*, 2017, Santos *et al.*, 2017). Studies in South Africa have shown that women report relatively chronic trajectories, while others show a natural remission over the perinatal period

(Garman *et al.*, 2019)(Chapter 3). Recent research has also conceptualised suicidal risk as cyclical or episodic (Bantjes *et al.*, 2016), and this had led to several studies investigating its longitudinal patterns (Prinstein *et al.*, 2008, Goldston *et al.*, 2016, Kasckow *et al.*, 2016). Using similar latent techniques, evidence also suggests different courses of suicidal risk over the life time (Goldston *et al.*, 2016, Madsen *et al.*, 2016). While these methods have not been used to assess the association between depression and suicidal behaviours over time, there is emerging evidence that the course of suicidal risk may be associated with the course of depression (Sokero *et al.*, 2006, Kerr *et al.*, 2013, Miller *et al.*, 2017).

To the best of our knowledge, the longitudinal investigation of depression in relation to suicidal risk has not been conducted among perinatal women in LMICs. So far, all studies on depression and suicidal risk among perinatal women in South Africa have been cross-sectional (Cooper *et al.*, 1999, Dewing *et al.*, 2013, Rochat *et al.*, 2013a, Onah *et al.*, 2017). While these have been useful in identifying at-risk groups, longitudinal studies would be helpful in understanding the relationship between depression and suicidal behaviours over time, especially given the heterogenous trajectories of depressive symptoms. This would indeed have direct implications on the treatment and follow-up of perinatal women presenting with either depressive symptoms. The present paper tries to address this gap by investigating the longitudinal association between depressive symptoms and suicidal risk among perinatal women living in a low-resource setting in South Africa, who are at risk for depression during pregnancy. The objectives of the study were to identify whether change in depressive symptom severity was associated with change in suicidal risk over time, and whether this association varied depending on age, stage in the perinatal stage and depressive symptom trajectory.

5.3. Methods

5.3.1. Design

This study is a secondary analysis of data collected for an individual randomised controlled trial (RCT) among pregnant women living in Khayelitsha, a peri-urban township settlement near Cape Town, South Africa. The RCT's objective was to assess the effectiveness of a six-session task-shared psychological intervention, delivered by community health workers (CHW), to treat perinatal depressive symptoms. No significant differences in depressive symptoms or suicidal risk were found over time (Lund *et al.*, Under review), so both arms were combined into one sample for the purpose of the present study. The RCT methods were described previously (Lund *et al.*, 2014), and are briefly summarised here.

5.3.2. Participants

Pregnant women were approached during their first antenatal visit in one of two antenatal clinics in Khayelitsha. Participants recruited into the RCT were 18 years or older, no more than 28 weeks pregnant, spoke isiXhosa, lived in Khayelitsha, and scored 13 or above on the Edinburgh Postnatal Depression Scale (EPDS; (Cox *et al.*, 1987)). The EPDS has been validated among isiXhosa-speaking women in South Africa, and a cut-off of 13 suggests high risk for depression (De Bruin *et al.*, 2004)(Lawrie et al. 1998). A total of 425 participants were enrolled into the RCT from October 2013 to October 2014. Six participants were wrongly enrolled as they did not meet the inclusion criteria (not pregnant or not isiXhosa-speaking), and 41 participants reported a pregnancy or baby loss during the study – these participants were excluded from the present analysis. The final sample therefore consisted of 384 participants.

5.3.3. Procedure

Once enrolled, participants were randomised into the psychological treatment or enhanced usual care (three monthly phone calls). All participants received the same routine antenatal care at the clinics. The baseline assessment was conducted at the clinic on the day of recruitment, and participants were followed-up at eight months gestation, and again at three months and 12 months postpartum. All assessments were conducted by trained fieldworkers who were blind to the participants' allocation arm. Follow-up assessments were conducted at home or at the clinic, depending on the participants' preference. Data were collected using mobile devices (www.mobenzi.com).

5.3.4. Instruments

The assessment instruments were translated to isiXhosa and back-translated into English by two independent translators. Demographic and socio-economic characteristics were collected during the baseline assessment, including age, highest education level, as well as employment, partner status and HIV status. Each assessment also included a range of measures covering social and health-related measures (see Appendix D). Those pertaining to the present study are presented here.

Suicidal ideation and behaviours

The Mini International Neuropsychiatric Interview (MINI) 6.0 (Sheehan *et al.*, 1998) Suicidality module was used to assess suicidal behaviours in the past month. The module is a structured diagnostic interview based the Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria. It

comprises 13 questions covering a range of suicidal behaviours, including ideation and self-harm. Scores range from 0 to 76; greater scores suggest greater suicidal risk. According to the MINI guidelines, a score of 9 to 16 suggests a moderate risk of suicide, while a score of 17 or more suggests high risk (Sheehan and Lecrubier, 2010). For the purpose of this study, the main outcome was a score of 9 or above, denoting moderate suicidal risk. Participants' responses to the items relating to the presence of ideation, plans or attempts in the past month were also noted. The MINI 6.0 has been used across many different settings and populations, including among postnatal women from Khayelitsha (Dewing *et al.*, 2013) and among pregnant women from another township settlement near Cape Town (Onah *et al.*, 2017).

Depressive symptoms

Depressive symptoms were assessed using a revised version of the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), adapted for use by trained fieldworkers for the RCT specifically. The HDRS is a 17-item rating scale assessing symptoms in the past two weeks; greater scores suggest greater symptom severity. The revised version of the HDRS has been validated in this population (Davies *et al.*, Under review), and shows adequate test-retest validity. To avoid circularity (Sokero *et al.*, 2006, Miller *et al.*, 2017), the suicide item was excluded from the HDRS total score in the present study - the maximum score was therefore 50. The internal consistency of the 16-item HDRS, measured using Cronbach's Alpha (α), was acceptable across timepoints (α= 0.67-0.79). The MINI 6.0 Major Depression Episode module was also administered to identify women with a current diagnosis of major depression.

5.3.5. Statistical analysis

Analyses were conducted in Stata version 14 (StataCorp, 2015). Baseline demographic and socio-economic characteristics of the sample, as well as suicide- and depression-related measures over time were investigated using measures of central tendency (means and standard deviations (SD)) for continuous variables, and frequencies and percentages for categorical variables. Differences in baseline characteristics between participants with full and partial data were assessed using the non-parametric Fisher's Exact Test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Generalised Estimating Equations (GEE) were used to assess the association between depressive symptoms (predictor) and suicidal risk (outcome) over time. This method of analysis was chosen as it adjusts standard errors for the correlation between multiple observations for each participant. Two

different suicidal risk outcomes were assessed: risk of suicide (score ≥ 9) and change in suicide score (change in *severity* of suicidal risk) from one assessment to the next. The latter was calculated for each participant by subtracting from the suicide score at each time point the suicide score from the previous assessment. A negative or positive change in suicide score from one assessment to the next therefore meant a decrease or increase in score, respectively.

The relation between change in HDRS score and change in suicide score was assessed in a series of four models. All models were adjusted for age of participant at baseline (<25 years, 25-34 years, or ≥35 years) and for 'trajectory group'. The latter variable categorised women into two latent groups, depending on the trajectory of their depressive symptoms over the perinatal period, identified in a previous study among the same sample using growth mixture modelling (Chapter 3): an *antenatal only* trajectory, with mild to moderate symptoms at recruitment, which decreased steadily from pregnancy to 12 months postpartum; and an *antenatal and postnatal* trajectory, characterised by moderate to severe symptoms, which decreased temporarily from pregnancy to 3 months postpartum, but increased again at 12 months postpartum. In the same study, the two trajectories showed different patterns of socio-demographic and clinical risk, including suicidal risk, thus justifying the inclusion of the variable among the possible confounders. The first of the four models included individual change in HDRS score as a predictor, which was calculated in the same way as change in suicide score. The second, third and fourth models also included the interaction of change in HDRS score with participant age at baseline (<25 years, 25-34 years, or ≥35 years), perinatal stage (pregnancy or postpartum period) and trajectory group (*antenatal only* or *antenatal and postnatal*), respectively.

Another series of four models were fitted with the same predictors but with suicidal risk (score ≥9) as an outcome. In addition to adjustments for age and trajectory group, the four models were adjusted for risk of suicide at the previous assessment. This way, each model assessed change in HDRS score from one assessment to the next in predicting risk of suicide at the next assessment above and beyond the risk of suicide at the previous assessment.

Secondary analyses were conducted to assess whether the association between HDRS and suicide scores varied depending on the direction of the change in HDRS scores. The same four models were computed again with change in suicide score as the outcome, this time adding a binary variable (decrease vs increase in HDRS score since the previous assessment) as an interaction term with change in HDRS score. This way, two coefficients of unit change in suicide score would be generated per model: one for a one-unit change decrease in HDRS score, and one for a one-unit increase in HDRS score.

An investigation into the correlation of change in suicide scores and suicidal risk over time suggested a different and random correlation pattern across timepoints, so an unstructured working correlation matrix was assumed and included as a covariate in all models. However, a robust variance estimator was used to adjust standard errors in case where the correlation matrix was not applicable. Analyses were based on observed data and assumed that data were missing completely at random. Dang *et al.* (Dang *et al.*, 2008) reviewed power and sample size calculations for GEE models, and given an attrition ranging between 12% and 24% over the three follow-up assessments and an unstructured within-subject correlation, the sample size of 384 participants was sufficient to achieve 80% power.

5.3.6. Ethics

This study was approved by the University of Cape Town (UCT)'s Human Research Ethics Committee (HREC REF 835/2015). The original RCT also received ethics approval from UCT (HREC REF 226/2011). Participants who scored 17 or above the MINI Suicidality module during data collection were automatically identified as being at high suicidal risk and were immediately referred to a psychiatric nurse in an adjacent community health centre.

Table 5.1 Baseline characteristics of the sample

	n	%
Gestation (mean, SD)	17.2	5.71
Age (mean, SD)	27.2	5.62
Age group		
18-24 years	134	34.9
25-34 years	204	53.1
35-45 years	46	12.0
Education level		
Less than high school completed	225	58.6
Completed high school or higher	159	41.4
Employment status		
Employed	177	46.1
Not employed	207	53.9
Partner status		
Lives with partner	130	33.9
Doesn't live with partner	254	66.1
HIV status (n=372)		
Negative	260	69.9
Positive	112	30.1

5.4. Results

The baseline socio-demographic characteristics of participants included in the study are presented in Table 5.1. Participants were on average 27 years old (SD = 5.62) and in their 18th week of pregnancy (SD = 5.71). The majority of participants had not completed high school (n = 225, 58.6%), were unemployed (n = 207, 53.9%) and did not live with their partners (n = 254, 66.1%). Nearly a third were HIV positive (n = 112, 30.1%). Of the 384 participants included in this study, 252 participants (65.6%) had complete data at all four timepoints, and 27 (7.0%) participants completed the baseline assessment only. Participants aged between 18 and 24 years were more likely to have incomplete data (at least one assessment missed) (n = 61, 45.5%) compared to participants aged at least 25 years (n = 71, 28.4%) (χ^2 = 11.3, p = 0.001). Unemployed participants (n = 81, 39.1%) were also more likely to have missed at least one assessment compared to employed participants (n = 51, 28.8%) (χ^2 = 4.5, p = 0.034).

At baseline, 87 (22.7%) participants scored at or above the moderate risk threshold on the MINI suicidality module; 76 reported suicidal ideation (19.8%) and 64 (16.7%) reported having made suicide plans in the past month (Table 5.2). Also, 3.4% (n = 13) of participants reported having made a suicide attempt in the past month. Among those who were at risk for suicide at baseline (n = 87, 22.7%), 59.7% (n = 52) reported moderate or severe depressive symptoms on the HDRS and 71.3% (n = 62) were diagnosed with depression on the MINI. However, among those diagnosed with depression (n = 157, 40.9%), only 39.5% (n = 62) were at risk for suicide. The proportion of participants at risk for suicide and reporting suicidal behaviours decreased steadily over the course of the study. The average HDRS scores and proportion of participants diagnosed with depression also decreased from recruitment to 8 months gestation but remained relatively stable over the remainder of the postpartum period.

Table 5.2 Descriptive statistics for depression and suicide outcomes over time

	Baseline (N = 384)		8 months gestation (N = 290)		3 months post-partum (N = 337)		12 months post-partum (N = 320)	
	n	%	n	%	n	%	n	%
HDRS score (mean, SD)	15.2	4.44	12.6	4.80	9.6	4.66	10.1	4.65
Diagnosis of depression	157	40.9	67	23.1	58	17.2	74	23.1
Suicide score (mean, SD)	7.8	15.4	3.2	9.02	2.1	7.39	1.7	6.23
Moderate to high suicidal risk [a]	87	22.7	28	9.7	14	4.2	9	2.8
Suicidal ideation	76	19.8	28	9.7	12	3.6	8	2.5
Suicide plans	64	16.7	18	6.2	10	3.0	8	2.5
Suicide attempt	13	3.4	3	1.0	2	0.6	1	0.3

[a] Defined as a score of 9 or more (MINI 6.0 suicidality module); SD=Standard deviation.

Table 5.3 Generalised Estimation Equations predicting change in suicide score from change in HDRS score, age, perinatal stage and depressive symptom trajectories groups

Predictors	Model 1 (Change)		Model 2 (Change x age)		Model 3 (Change x perinatal stage)		Model 4 (Change x trajectory)	
	aβ (SE)	95%CI	aβ (SE)	95%CI	aβ (SE)	95%CI	aβ (SE)	95%CI
Change in HDRS score	**0.57 (0.11)**	**0.35; 0.78 *** **	0.68 (0.15)	0.38; 0.98 ***	0.63 (0.23)	0.17; 1.09 **	0.50 (0.12)	0.27; 0.73 ***
Age								
18-24	Ref	-	Ref	-	Ref	-	Ref	-
25-34	0.72 (0.72)	-0.68; 2.13	0.55 (0.68)	-0.80; 1.89	0.69 (0.72)	-0.73; 2.11	0.73 (0.71)	-0.67; 2.13
35-45	2.34 (1.01)	0.72; 3.96 **	1.43 (0.98)	-0.50; 3.35	2.30 (0.83)	0.67; 3.93 **	2.38 (0.83)	0.75; 4.01 **
Trajectory								
Antenatal only	Ref	-	Ref	-	Ref	-	Ref	-
Antenatal and postnatal	-0.86 (1.15)	-3.12; 1.40	-0.89 (1.16)	-3.16; 1.37	-0.67 (1.14)	-2.91; 1.56	-0.36 (1.13)	-2.57; 1.85
Perinatal stage								
Pregnancy	-	-	-	-	Ref	-	-	-
Postpartum	-	-	-	-	2.26 (1.15)	-0.01; 4.52	-	-
Change x age								
18-24	-	-	**Ref**		-	-	-	-
25-34	-	-	**-0.08 (0.22)**	**-0.52; 0.36**	-	-	-	-
35-45	-	-	**-0.53 (0.26)**	**-1.04; -0.03 ***	-	-	-	-
Change x perinatal stage								
Pregnancy	-	-	-	-	**Ref**		-	-
Postpartum	-	-	-	-	**-0.16 (0.23)**	**-0.62; 0.30**	-	-
Change x trajectory								
Antenatal only	-	-	-	-	-	-	**Ref**	**-**
Antenatal and postnatal	-	-	-	-	-	-	**0.38 (0.33)**	**-0.26; 1.02**

NOTE: Coefficients represent the change in suicide score per unit change in HDRS score; Coefficients of interests are in bold; CI=confidence intervals; HDRS=Hamilton Depression Rating Scale; SE=Standard error; * p<0.05; ** p<0.01; *** p<0.001.

The results of the GEE predicting change in suicide scores and risk of suicide are presented in Tables 5.3 and 5.4. After controlling for age and trajectory group, change in HDRS scores was associated with both suicide outcomes: a one-point unit change in HDRS score from one assessment to the next was associated with a 0.57 point unit change in suicide score (95%CI 0.35, 0.78; p < 0.001); it was also associated with greater odds of being at moderate risk for suicide (adjusted odds ratio (aOR) = 1.15; 95%CI 1.09, 1.22; p < 0.001) after controlling for risk of suicide at the previous assessment.

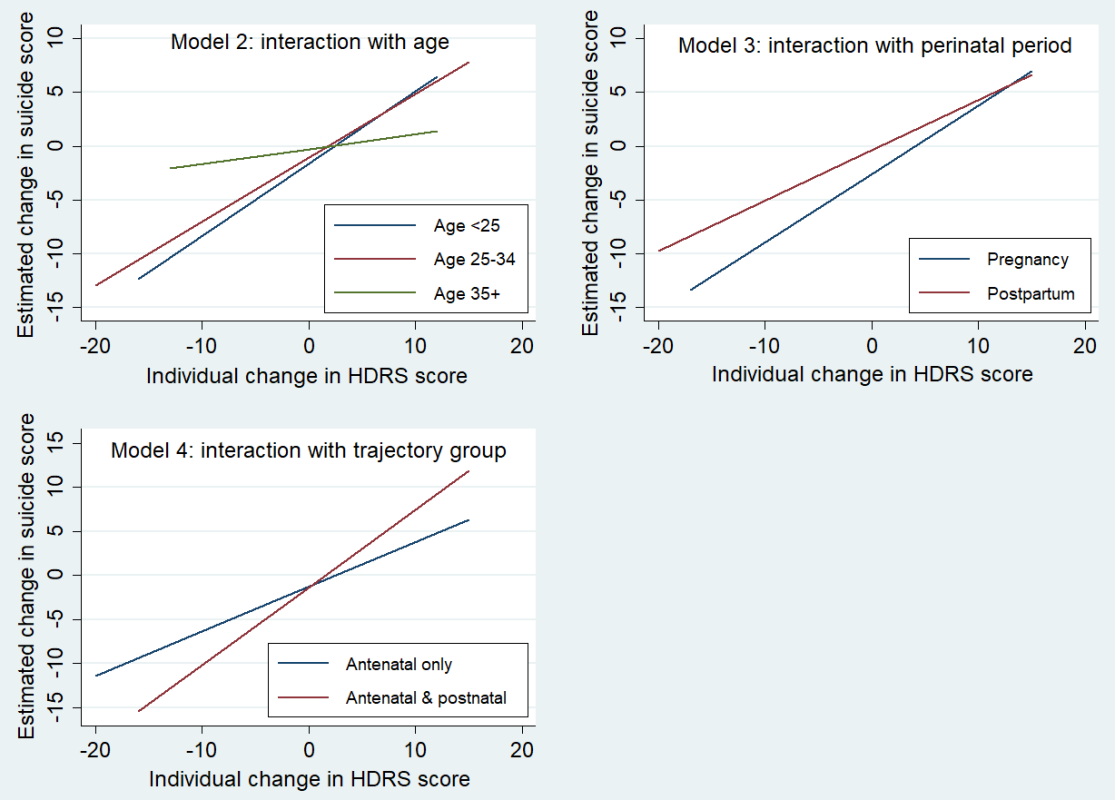

Figure 5.1 Interaction of change in HDRS scores with age, perinatal stage and trajectory group in predicting change in suicide scores

The effect of age, perinatal stage and trajectory group on the association between individual change in HDRS score and individual change in suicide scores are presented in Figure 5.1. Age was a significant effect modifier: a one-point unit change in HDRS score was associated with a 0.68-point (95%CI 0.38, 0.98; p < 0.01) and a 0.60-point (95%CI 0.27, 0.92; p < 0.001) unit change in suicide score among the younger (18 to 24-year olds) and the middle-age participants (25 to 34 years), respectively. However, change in HDRS scores was not associated with change in suicide scores among the older group (35-45 years old) (adjusted (a)β = 0.16; 95%CI -0.26; 0.55; p > 0.05); the difference in slope between the older and younger groups was significant (aβ = -0.53, 95%CI -1.04, -0.03; p < 0.05). A similar trend was noted when assessing risk of suicide: the odds of being at risk for suicide were 1.17 times greater with

every one-point increase in HDRS score, both among the younger group (95%CI 1.07, 1.27 $p < 0.01$) and among the middle-age participants (95%CI 1.08, 1.26; $p < 0.001$). No association was found among the older group (aOR = 1.04; 95%CI 0.85, 1.27; $p > 0.05$). The difference in odds across age groups failed to reach statistical significance, however.

There was no effect of perinatal stage on the association between change in HDRS scores and change in suicide scores (aβ = 0.16; 95%CI -0.62; 0.30; $p > 0.05$) or suicidal risk (aOR = 0.93; 95%CI 0.83; 1.05; $p > 0.05$). There was also no effect of the trajectory group on the association between change in HDRS scores and change in suicide score (aβ = 0.38; 95%CI -0.26; 1.02; $p > 0.05$), but there was an effect of trajectory group on the association between change in HDRS scores and suicidal risk (aOR = 0.91; 95%CI 0.82; 1.00; $p < 0.05$): the odds of being at risk for suicide with a one-unit change in HDRS score were greater among the *antenatal only* trajectory group (aOR = 1.19; 95%CI 1.10; 1.29; $p < 0.001$) compared to the *antenatal and postnatal* trajectory group (aOR=1.08; 95%CI 1.02; 1.15; $p < 0.01$).

The secondary analyses indicated that a one-unit decrease in HDRS score was associated with a -0.72 unit decrease in suicide scores (95%CI -0.31; -1.14; $p < 0.01$), but a one-unit increase in HDRS score was not associated with a change in suicide score (aβ = 0.24; 95%CI -0.30; 0.79; $p > 0.05$). Neither age, time in the perinatal stage nor trajectory group had an effect on these associations, however. Interestingly, while a one-unit decrease in HDRS score was associated with a 0.59 (95%CI 0.06; 1.11; $p < 0.05$) and 0.84 (95%CI 0.23; 1.45; $p < 0.01$) unit decrease in suicide score among younger and middle-age participants, respectively, this was not associated with a decrease in suicide score among the older participants (aβ = 0.32; 95%CI -0.24; 0.88; $p > 0.05$). Similarly, a one-unit decrease in HDRS score was associated with a 0.67-unit decrease in suicide score among the *antenatal only* trajectory group (95%CI 0.23; 1.11; $p < 0.01$), but this association was only marginal among the *antenatal and postnatal* trajectory group (aβ = 0.95; 95%CI -0.09; 1.99; $p > 0.05$).

Table 5.4 Generalised Estimation Equations predicting suicidal risk from change in HDRS score, age, perinatal stage and depressive symptom trajectories groups

Predictors	Model 1 (Change)		Model 2 (Change x age)		Model 3 (Change x perinatal stage)		Model 4 (Change x trajectory)	
	aOR (SE)	95%CI	aOR (SE)	95%CI	aOR (SE)	95%CI	aOR (SE)	95%CI
Change in HDRS score	**1.15 (0.03)**	**1.09; 1.22 *** **	1.17 (0.05)	1.07; 1.27 **	1.21 (0.05)	1.10; 1.32 ***	1.19 (0.05)	1.10; 1.29 ***
Age								
18-24	Ref	-	Ref	-	Ref	-	Ref	-
25-34	0.79 (0.25)	0.42; 1.49	0.80 (0.26)	0.42; 1.50	0.67 (0.23)	0.34; 1.33	0.80 (0.25)	0.43; 1.49
35-45	0.58 (0.38)	0.16; 2.11	0.69 (0.43)	0.20; 2.31	0.54 (0.37)	0.14; 2.07	0.61 (0.39)	0.17; 2.14
Trajectory								
Antenatal only	Ref	-	Ref	-	Ref		Ref	
Antenatal and postnatal	2.53 (1.14)	1.05; 6.13 *	2.60	1.08; 6.25 *	3.75 (1.83)	1.44; 9.76 **	2.83 (1.14)	1.28; 6.24 *
Suicidal risk (previous assessment)								
Low	Ref	-	Ref	-	Ref	-	Ref	
High	10.47 (3.45)	5.48; 19.99 ***	11.19 (3.60)	5.95; 21.03 ***	5.58 (2.08)	2.68; 11.59 ***	10.08 (3.36)	5.25; 19.36 ***
Perinatal stage								
Pregnancy	-	-	-	-	Ref		-	-
Postpartum	-	-	-	-	0.28 (0.10)	0.14; 0.54 ***	-	-
Change x age								
18-24	-	-	**Ref**	**-**	-	-	-	-
25-34	-	-	**1.00 (0.06)**	**0.89; 1.13**	-	-	-	-
35-45	-	-	**0.89 (0.10)**	**0.72; 1.11**	-	-	-	-
Change x perinatal stage								
Pregnancy	-	-	-	-	**Ref**	**-**	-	-
Postpartum	-	-	-	-	**0.93 (0.06)**	**0.83; 1.05**	-	-
Change x trajectory								
Antenatal only	-	-	-	-	-	-	**Ref**	**-**
Antenatal and postnatal	-	-	-	-	-	-	**0.91 (0.04)**	**0.82; 1.00 ***

NOTE: Adjusted odds ratios represent the odds of being at risk for suicide for every unit change in HDRS score; Coefficients of interests are in bold; aOR=adjusted odds ratios; CI=confidence intervals; HDRS=Hamilton Depression Rating Scale; SE=Standard error; * p<0.05; ** p<0.01; *** p<0.001.

5.5. Discussion

Our study sought to investigate the longitudinal association between depressive symptoms and suicidal risk among perinatal women at risk for depression during pregnancy and living in a low-income township settlement near Cape Town. Overall, our results indicate that change in depressive symptom severity was associated with change in severity of suicidal risk. However, this association was only present when depressive symptom scores decreased. In other words, any improvement in depressive symptoms was likely to be accompanied by an improvement in suicidal risk severity, but a worsening of depressive symptoms was not associated with change in suicidal risk severity. One may argue that this may reflect the protective perinatal stage that has been mentioned in previous research (Lindahl *et al.*, 2005, Fuhr *et al.*, 2014), especially given that this pattern of association did not differ from pregnancy to the postpartum period. A longer follow-up would have enabled us to assess whether this association differed after 12 months postpartum compared to during the perinatal stage.

The longitudinal association between depressive symptoms and severity of suicidal risk was moderated by age and trajectory type: a decrease in depressive symptoms was associated with a decrease in severity of suicidal risk among women aged 18 to 34 years and among those whose depressive symptoms decreased over the course of the perinatal period. This was not the case, however, among older women and those with more severe depressive symptoms throughout the perinatal period. One explanation for this finding could be that for some women, suicidal risk took longer to abate following a decrease in depressive symptoms; a possibility we could not assess since we analysed simultaneous change in depressive symptoms and severity of suicidal risk, from one assessment to the next. Indeed, our previous work indicated that women from the *antenatal and postnatal* trajectory group were at higher risk of suicide at baseline (Chapter 3). And yet a study in the US among adults suffering from depression and on antidepressants showed that it took longer for suicidal behaviours to subside, following a decrease in depressive symptoms, among those who initially reported greater risk of suicide (Szanto *et al.*, 2003).

Alternatively, our findings could indicate that depression and suicidal risk are not necessarily associated for all perinatal women. For instance, women belonging to the *antenatal and postnatal* trajectory group reported poorer social and economic circumstances and poorer clinical features during pregnancy (Chapter 3). Given the common risk factors for suicide and depression, the results could indicate that these risk factors had a direct impact on women's course of suicidal risk, independent of depressive symptoms. Suicidal risk among the *antenatal only* trajectory group, on the other hand, may not necessarily be an indicator of future suicidal behaviour but reflect transient

endorsements of suicidal thoughts as an expression of general initial distress associated with pregnancy (e.g. HIV positive status, lack of support from partner or family), which subsides alongside depressive symptoms as women and their families accept the pregnancy. In the present study, the incidence of suicidal ideation, plan or attempt was too small to meaningfully assess the association between such behaviours and depressive symptoms over time. It is therefore not possible to say whether the pattern of association found in our study relate to suicide risk in general, or whether it is specific to suicidal thoughts or actual suicidal behaviour, such as self-harm or suicide attempts. However, there is evidence from a nationally representative South African survey suggesting that only 31.7% and 11.2% of individuals reporting suicidal ideation eventually make a suicide attempt, with and without a plan, respectively, and that anxiety and impulse-related disorders were stronger risk factors for suicide attempts among people with suicide ideation than major depression (Joe *et al.*, 2008).

In fact, there is emerging evidence, mostly from high-income countries, that there are heterogeneous profiles of symptoms among people diagnosed with depression, which differ in terms of severity and endorsement of anxiety and self-harm symptoms (Putnam *et al.*, 2017). While this was beyond the scope of this study, it could be that the lack of association between depressive symptoms and suicidal risk among older women or those who report more severe and chronic depressive symptoms, such as in the *antenatal and postnatal* trajectory group, reflects a type of depressive symptomatology which is independent of suicidal ideation.

Altogether, our findings indicate that depressive symptoms and risk of suicide were only associated when depressive symptoms decreased, and that among younger women and among those who showed milder depressive symptoms over the course of the perinatal period. This supports the idea that, among women at risk for depression during pregnancy, depression and suicidal risk are overlapping but reasonably distinct entities. This has direct implications on the treatment and monitoring of perinatal women at risk for depression over time – in both research and clinical contexts. Indeed, this means that women may still be at risk for suicide even if depressive symptoms decrease. It is therefore essential to assess both phenomena independently, as suggested by Nock *et al.* (2009) in their global review of the literature on mental disorders and suicidal behaviours.

In our study, of the 23% of the pregnant women recruited who were at risk for suicide, over a quarter did not have a diagnosis of depression. This contrasts with Dewing *et al.* (2013)'s study, where 8% of pregnant women from Khayelitsha reported mild to severe risk of suicide on the MINI suicidality module, and with Onah *et al.* (2017)'s study, where 18% of pregnant women living in a nearby

township settlement reported suicidal ideation or behaviour, at least half of whom did not suffer from depression, anxiety or personality disorder. The different profile of suicidal risk reported in our study is likely due to the high-risk nature of the sample, since all women screened positive on the EPDS and thus at risk for depression. We acknowledge that women were screened with the EPDS which included a suicide/self-harm item, so the sample may be biased. However, when the self-harm item was excluded from the total EPDS score at recruitment, only 5% of women score below the cut-off of 13 (between 10 and 12). So, our sample is likely to still be a high-risk group for depression, regardless of suicidal risk. Given the above evidence, we could assume, then, that the identification of depression and suicidal risk should also be done separately, irrespective of their depressive symptom severity during pregnancy.

Some have argued that assessing suicidal risk is less reliable when done in the context of a screening tool for depression, compared to when it is assessed independently (Lindahl *et al.*, 2005). However, the risk of suicide in research studies is often measured using a single item which is included in most screening tools used for perinatal depressive symptoms (Cooper *et al.*, 1999, Dewing *et al.*, 2013), which is not ideal given our findings. Rochat *et al.* (2013a) reported that the self-harm item on the EPDS had good sensitivity and specificity among women living in a rural area in Kwa-Zulu Natal, South Africa. This, however, was not the case in the present study, where neither the EPDS nor the HDRS suicide items were well correlated with suicidal ideation or suicidal risk assessed with the MINI (results not presented here).

There are no formal identification or monitoring mechanisms for depression or suicidal risk in clinical settings in South Africa (Department of Health, 2015), other than when conducted through NGOs or donor agencies (Honikman *et al.*, 2012), most of which use depression screening tools similar to the EPDS. However, three screening questions are to be included in the next version of the maternity case records, which are forms that are completed by nurses for all pregnant women at each antenatal visit (Appendix C). Two of these questions relate to mood and one to suicidal behaviours, and will be asked by nurses only in circumstances where a referral system and mental health services are available. Women who endorse the suicide item, suggesting the presence of suicidal ideation and plan, will be referred immediately, regardless of their responses on the other two mood-related questions. This tool could be used as a way to identify and monitor women at risk for depression or suicide, though the sensitivity of a single item in identifying women at risk for suicide remains to be assessed.

5.5.1. Limitations

Our study has several limitations which should be acknowledged. First, both depressive symptoms and suicidal behaviours were self-reported, which is known to be less reliable than formal assessments (Bachmann, 2018). Second, this study was exploratory in nature, which led to multiple comparisons to assess a range of child outcomes at 18 and 36 months postpartum. The risk of type I error should therefore be kept in mind when interpreting the present findings. Third, cultural context is very important in the aetiology of suicidal behaviours (Bantjes *et al.*, 2016, Turecki and Brent, 2016), so our findings are unlikely to be generalisable to other LMICs, or other populations within South Africa. Fourth, the incidence of suicidal ideation, plan or attempt was too small to meaningfully assess the association between such behaviours and depressive symptoms over time. It is therefore not possible to say whether the pattern of association found in our study extends to self-harm or suicide attempts. In fact, the prevalence of suicidal behaviours decreased steadily over the study period. This 'regression to the mean', a phenomenon commonly seen in RCTs, could be avoided in future studies assessing symptoms in a less controlled setting and among a bigger sample. A fifth limitation is that the aim of our paper was not to identify risk factors involved in the complex pathways to suicidal behaviours, so we did not control for any demographic variables, other than age, as suggested in previous reviews of the literature (Bantjes *et al.*, 2016, Iemmi *et al.*, 2016). However, we did run post-hoc analyses to ensure that the modifying effect of age was not confounded by number of children in the mothers' care – a factor which could become decisive for women reporting suicidal ideation. Moreover, given the comorbidity of depression and anxiety among perinatal populations, globally and in South Africa (Barthel *et al.*, 2017, Biaggi *et al.*, 2016, Redinger *et al.*, 2017), it is possible that the association found between depressive symptoms and suicidal risk could be driven by anxiety symptoms, which were not measured in this study. Similarly, while the study focused solely on the relationship between depression and suicidal risk, it is possible that other mental disorders, such as bipolar disorder or schizophrenia, may explain the course of suicidal risk better over the perinatal period. And finally, GEE is a method of analyses that generates population-average estimates. Given the complex aetiology of depressive symptoms and suicidal behaviours, other methods of analysis, such as multilevel modelling, could provide some valuable insights into individual differences in the longitudinal association between depressive symptoms and severity of suicidal risk. Also, estimating risk ratios would have been preferable, rather than odd ratios which are subject to fallacies of variation across prevalence. This was not possible, however, given the complexity and non-convergence of models.

5.6. Conclusions

Our study sheds light on the association between depressive symptoms and suicidal risk over the perinatal period and highlights the importance of considering depression and suicide as overlapping but relatively independent phenomena. Our study also contributes towards identifying high-risk groups for preventive strategies among low-income perinatal women at risk for depression or suicide. Given that suicidal ideation remains one of the strongest predictors of suicide attempts within a year of ideation onset among South Africans (Joe *et al.*, 2008), it is essential that pregnant and postnatal women at risk for suicide are identified and monitored independently from risk of depression, so that suicidal behaviours are prevented, and the related health and economic burden avoided. Including screening for suicidal risk as part of antenatal care is one step in the right direction, but further efforts should go into understanding the pathways towards suicidal behaviours and depressive symptoms among high-risk perinatal groups in LMICs.

Chapter 6. Discussion

This Chapter summarises the main findings reported in Chapters 2 to 5. With the limitations of the studies in mind, recommendations for future research are then made. Given the current South African health system and guidelines that are in place, recommendations for improving perinatal mental health care in South Africa are provided and informed by current relevant literature in the field of public mental health.

6.1. Overview of findings

6.1.1. Trajectories of perinatal depressive symptoms

Chapter 2 reviewed the evidence of studies making use of growth curve mixture modelling (GCMM) methods to identify trajectories of perinatal depressive symptoms. All studies found in the literature were conducted in high-income countries (HICs), and while the samples were diverse, and the timing and frequency of assessments varied greatly, there seem to be a pattern in the types of trajectories reported. The three most common trajectories identified were 1) a 'low-risk' trajectory, characterised by chronically low levels of depressive symptoms throughout the perinatal period (most often the majority of the sample); 2) a 'high-risk' trajectory, characterised by chronically high levels of depressive symptoms; and 3) an 'antenatal' trajectory, with greater levels of symptoms antenatally, which naturally abate by the time of birth.

The chronic 'high-risk' trajectory was also identified among the general perinatal population from Khayelitsha in Chapter 4, and similarly to studies reviewed in Chapter 2, this trajectory represented only a minority of the sample (4.5%). A similar trajectory was also reported in Chapter 3, among women initially at risk for depression during pregnancy, though symptoms levels declined temporary until three months postpartum. This indicates that in both HICs and low- and middle-income countries (LMICs), there is a group of women who are consistently at risk for depression throughout the perinatal period. The advantage of specifically focusing on pregnant women at high-risk for depression in Chapter 3 was that it allowed the identification of an 'antenatal' trajectory type, also identified in the systematic review, where the majority of women with initially high levels of depressive symptoms showed a natural remission to mild levels later in the perinatal period. In Chapter 4, all women were recruited regardless of their initial level of depressive symptoms, and only a minority reported initially severe symptoms during pregnancy. So, there may not have been enough power for this type of latent

trajectory to be detected, and women showing this course of symptoms may have instead been allocated to the low-risk trajectory. Indeed, unlike the low-risk trajectories reported in the systematic review, the low-risk trajectory in Chapter 4 was still characterised by mild symptoms during pregnancy, suggesting that women with chronically low levels of depressive symptoms and those reporting antenatal symptoms only were combined into one latent group. This is one of the criticisms often reported on the use of GCMM, in that trajectory allocation is not observed, but estimated based on probabilities (Ram and Grimm, 2009). Despite individual variability being allowed when modelling latent trajectories, depending on the type of GCMM method used, there is still a margin of error between the women's allocated trajectory and their observed course of symptoms. This error increases when the overall sample size is small, since models with fewer trajectories are usually preferred, at the expense of additional smaller, but perhaps clinically relevant trajectories.

It is surprising that only two studies in the systematic review in Chapter 2 reported an *early postpartum* trajectory (Mora *et al.*, 2009, Christensen *et al.*, 2011). Indeed, this trajectory typically reflects the course of symptoms expected for postnatal depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Statistical Classification of Diseases and Related Health Problems (ICD) classifications, with onset within one or two months of giving birth. This trajectory was also reported in Chapter 4 and represented 14% of the sample. It was not, however, reported in Chapter 3, since only women at risk for depression were initially recruited. However, the three-class model solution generated with GMM in Chapter 3 (Table 3.3) did include a trajectory which resembled the *early postpartum* trajectory, which was characterised by moderate levels of symptoms during pregnancy, which increased to severe levels in the early postpartum period (see Appendix J for a graphical representation of the trajectories). While fit indices were nearly identical, this class only comprised 16 participants (4% of the sample), and so for reasons of parsimony, the two-class model was selected as the optimal model instead. Again, further research with larger samples is warranted to assess whether this trajectory may actually be clinically meaningful.

Another trajectory, which was reported by two studies in Chapter 2 (Mora *et al.*, 2009, Vänskä *et al.*, 2011), was characterised by relatively low symptoms levels throughout pregnancy and the early postpartum period, which increased to severe levels at 12 to 24 months postpartum. Interestingly, this trajectory was also identified in Chapter 4, where 10% of women showed initially relatively low symptoms, which continued to decrease until six months postpartum, and increased again to levels as severe as those who showed chronically severe symptoms throughout the perinatal period. This highlights how women may still be at risk for perinatal depression later in the postpartum period, both in HICs and LMICs. The fact that this trajectory was also reported in HIC (Mora *et al.*, 2009, Vänskä *et*

al., 2011), however, means this course of symptoms may be a global phenomenon. Unfortunately, this type of trajectory may often be missed, since longitudinal studies tend to only assess depressive symptoms within the first few months after birth (Vliegen *et al.*, 2014), or investigate maternal depression in pre-school or school years. This also applies to findings reported in Chapter 3, where additional assessments beyond the 12-month postpartum mark may have indicated a change in the course of symptoms among the *antenatal only* or *antenatal and postnatal* trajectories. The presence of a 'late postpartum' trajectory in Chapters 2 and 4, coupled with the fact that relatively few studies reported trajectories with increased symptoms in the early postpartum period, point to the possibility that the current definition and timing criterion in DSM and ICD classifications for postpartum depression may not be ideal. This also supports a current line of thought advocating for a change in the definition of perinatal depression, and the need to take on a more dimensional view of depression (Jacob and Patel, 2014, Patel, 2017), where depressive symptoms should be investigated as a continuous risk for the mother and her child, regardless of time of onset (Wisner *et al.*, 2010, Sutter-Dallay *et al.*, 2011).

The trajectories identified in Chapter 4 corroborate those reported in a concurrent study in Côte d'Ivoire and Ghana (Barthel *et al.*, 2017) – to my knowledge, the only other study conducted in a LMIC. In Barthel *et al.* (2017)'s study, women were recruited three months before birth, and followed up at three, 12 and 24 months postpartum. Women's depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9) (Kroenke and Spitzer, 2002), another common screening instrument for depression, and three trajectories were identified through growth mixture modelling (GMM). All three resemble the *chronic low*, *early postpartum* and *late postpartum* trajectories identified in Chapter 4. The lack of a chronically 'high-risk' trajectory in Barthel *et al.* (2017)'s study may be due to the sampling criteria: by excluding all women who reported preterm births (<34 weeks) or having given birth to a baby of low birth weight (<2.5 kg), a high-risk group, with possibly greater depressive symptoms during pregnancy may have been excluded. Again, the *late postpartum* trajectory, referred to as 'recurrent risk' by the authors, shows how depressive symptoms may still worsen after 12 months postpartum – beyond the perinatal period as defined by the World Health Organization (World Health Organization, 2010).

Bearing in mind that the number and shape of trajectories identified are a function of the sample characteristics, as well as the modelling parameters employed to generate these trajectories, the findings from Chapters 2 to 4 provide valuable evidence that women do show heterogenous trajectories of perinatal depressive symptoms and that these may not be that different across regions. The fact that trajectories were associated with different risk factors in Chapters 2 to 4, and with

different child outcomes in Chapter 4 further, emphasises the clinical utility and veracity of the trajectories identified, and minimise the possibility that these only represented statistically-generated concepts, a limitation that Ram and Grimm (2009) have warned about with the use of GCMM. The findings relating to risk factors and child outcomes are discussed in more detail below.

6.1.2. Risk factors for trajectories of perinatal depressive symptoms

As reported in Chapter 2, the majority of risk factors assessed in relation to trajectories of perinatal depressive symptoms in the literature were proximal factors at the individual and interpersonal level, and included a range of demographic, social, clinical and personality characteristics. The fact that different risk factors were investigated across studies meant it was difficult to identify clear patterns of risk per type of trajectory. For example, Kuo *et al.* (2012) focused on quality of sleep and exercise, Mora *et al.* (2009) on emotional health and stress, whereas both Parade *et al.* (2014) and Ramos-Marcuse *et al.* (2010) focused on parenting and personality-related characteristics. All studies assessed differences in socio-demographic characteristics between trajectories, however, and even these did not consistently differentiate higher-risk trajectories (transient or chronic moderate or severe symptoms) from low-risk trajectories. No other patterns of risk could be identified by shape of trajectory.

In general, however, results from studies reporting relatively stable, or chronic trajectories throughout the perinatal period indicated that demographic, social and health-related risks were associated with trajectories showing more severe symptom levels, compared to trajectories at recruitment with low levels throughout pregnancy and postpartum period. These included age (Sutter-Dallay *et al.*, 2012b), ethnicity (Mora *et al.*, 2009), social support (Glasheen *et al.*, 2013), sleep difficulty during pregnancy (Kuo *et al.*, 2012, Kuo *et al.*, 2014) and anxiety or stress (Mora *et al.*, 2009, Sutter-Dallay *et al.*, 2012b). Given the stable nature of these studies' trajectories, such results support findings from cross-sectional studies assessing correlates of depressive symptom severity. The benefits or appeal of GCMM methods is that researchers can potentially identify factors which differentiate women with similar initial levels of depressive symptoms, which later change course – such as differentiating women with chronically low trajectories from women who only report depressive symptoms only later in the perinatal period (Chapter 4), or differentiating women whose symptoms naturally abate before giving birth, from those whose symptoms remain chronically severe throughout the perinatal period (Chapter 3). Clinically, being able to differentiate such groups would have huge implications on the identification of women at high risk for more severe or chronic symptoms. However, findings from Chapter 2 indicate that, while demographic, psychosocial and health-related factors did differentiate

such transient trajectories from chronic trajectories in Mora *et al.* (2009)'s study, this was not the case in other studies reporting both chronic and transient trajectories with similar levels of symptoms either during pregnancy or in the postpartum period (Sutter-Dallay *et al.*, 2011, Vänskä *et al.*, 2011).

More consistent results were reported among both low- and high-risk perinatal women in Khayelitsha in Chapters 3 and 4. First, none of the demographic characteristics (age, education level, marital status, employment status) were associated with trajectory type in either sample. Women allocated to the different trajectories in Chapter 4 also did not differ in terms of parity, or whether the pregnancy was planned or wanted. These findings are supported in Barthel *et al.* (2017)'s study among perinatal women in West Africa, where authors report no associations with age, education, parity or marital status. Second, relative wealth was also not associated with trajectory type in either Chapter 3 or 4. However women allocated to the *antenatal and postnatal* trajectory in Chapter 3 were more likely to report food insecurity. This supports past evidence in South Africa suggesting that food insecurity may be a better indicator for risk of depression in impoverished areas (Tsai *et al.*, 2012, Dewing *et al.*, 2013, van Heyningen *et al.*, 2016, Abrahams *et al.*, 2018). In their review, Cooper *et al.* (2012) also indicate that food insecurity may be a more sensitive measure when assessing the effects of poverty on depression, compared to other more non-specific measures such as socio-economic status. Interestingly, relative socio-economic status in Barthel *et al.* (2017)'s study, which was calculated as above or below the average economic level within the sample, also was not associated with trajectories. However, high economic stress was associated with the 'recurrent risk' trajectory, which resembles the *late postpartum* trajectory in Chapter 4. It seems, therefore, that demographic characteristics at recruitment are not associated with the course of depressive symptoms during the perinatal period in Khayelitsha.

Third, in both Chapters 3 and 4, low social support and alcohol use during pregnancy were associated with the 'high-risk' trajectories – the *antenatal and postnatal* (Chapter 3) and *chronic high* trajectories (Chapter 4). Low social support had also been reported as a risk factor for a chronic but moderate trajectory among American women in Glasheen *et al.* (2013)'s study (Chapter 2): those with higher social support were 51% less likely to be in this higher risk trajectory. This was not the case in Barthel *et al.* (2017)'s study, however, where women's retrospective reports of social support throughout the perinatal period was not associated with any of the trajectories.

Alcohol use during pregnancy had not been investigated as a risk factor among any of the studies included in the systematic review in Chapter 2. However, given the high prevalence of Foetal Alcohol Syndrome in the Western Cape (May *et al.*, 2013) and the high comorbidity between alcohol use

disorder and depression (Boden and Fergusson, 2011), it seemed sensible to investigate this specific factor in relation to trajectories among women living in Khayelitsha. The fact that alcohol use during pregnancy was identified as a risk factor for both high-risk trajectories in Chapters 3 and 4 highlights how essential it is to also screen for alcohol and substance use during pregnancy, in addition to depression. In a pilot study conducted in township settlements in Cape Town, Sorsdahl *et al.* (2014) assessed the feasibility of HIV counsellors screening for alcohol and substance use during women's first antenatal visit at a clinic. Authors highlighted the likely underreporting of alcohol use among pregnant women out of fear of stigma and social services, and the need to promote a safe environment to improve disclosure. Interviews with midwives and HIV counsellors indicated, however, that such identification strategies were feasible and acceptable to the clinic staff. Further implementation research is therefore needed to assess whether screening for alcohol use and providing education on the effects of alcohol consumption on the foetus can be scaled up in South Africa.

Fourth, IPV was identified as a risk factor in both Chapter 3 and 4, but the associations with trajectory type was less clear. Women reporting IPV during pregnancy were at higher risk of belonging to the *antenatal and postnatal* trajectory in Chapter 3, but to the *late postpartum* trajectory in Chapter 4. While it is understandable that IPV is associated with depressive symptoms, as IPV often leads to women's social, emotional and physical isolation (Campbell and Lewandowski, 1997), it is unclear how IPV during pregnancy would be associated with an increase in symptoms later in the postpartum period – a similar trait for both trajectories in Chapters 3 and 4. In the present thesis, only predictors at baseline were investigated to identify groups of women with higher-risk trajectories. However, previous evidence suggests that severity of IPV increased as the pregnancy progressed among pregnant women in Soweto, South Africa (Dunkle *et al.*, 2004). Thus, future research is needed to examine the role of IPV as a varying predictor, and its effect on the rate of change in depressive symptoms over the perinatal period.

Finally, in both Chapters 3 and 4, the high-risk trajectories were associated with the most risk factors, suggesting women allocated to these trajectories were likely to be experiencing multiple stressors. In Chapter 3, women assigned to the *antenatal and postnatal* symptom trajectory were more likely to be food insecure, experience IPV, report lower perceived social support, be more functionally impaired, report heavy drinking during pregnancy, have a past and current diagnosis of depression, and be at high risk for suicide. In Chapter 4, women with chronically severe symptoms were more likely to report lower social support, an unwanted pregnancy and risky drinking during pregnancy. This supports the ecological model described in Chapter 1 (Bronfenbrenner, 1994), indicating that mental

health cannot be separated from contextual social and economic influences, and that frequently these influences cluster to increase risk in vulnerable populations. This is especially important to note, given that women allocated to the *antenatal and postnatal* (Chapter 3) and *chronic high* (Chapter 4) trajectories had, on average, relatively similar levels of depressive symptoms during pregnancy as women whose symptoms showed a natural remission (Chapter 3) or whose symptoms initially decreased and only increased later in the postpartum period (Chapter 4). A measure of depressive symptoms only during pregnancy would therefore not have differentiated women who continued to experience symptoms of depression compared to those who showed a natural remission.

In neither Chapter 3 or 4 was HIV positive status associated with the high-risk trajectories. Because of the high prevalence of HIV and treatment coverage in South Africa (HIV/AIDS, 2016), a positive status may no longer be seen as a death sentence and is less stigmatising. However, in Chapter 4, HIV was a risk factor for the *early postpartum* trajectory. As explained in the Chapter, the increase in depressive symptoms in the early postpartum period may be linked to the practical and emotional impact of the new status once the baby is born (Rochat *et al.*, 2006). Indeed, the peak of depressive symptoms in the early postpartum period could indicate the mothers' adjustment to dealing with a chronic illness in conjunction with having to care for a new baby. This is an important finding and a phenomenon that HIV counsellors should be aware of as they provide guidance on medication adherence and during Prevention of Mother-to-Child Transmission interventions.

6.1.3. Trajectories of perinatal depressive symptoms and child outcomes

Further supporting the qualitative difference in trajectories identified in Chapter 4 is the identification of differences in child development outcomes across trajectories. To my knowledge, Chapter 4 reports the first study in Sub-Saharan Africa to compare child growth and development in relation to trajectories of perinatal depressive symptoms generated through GCMM. Results indicate that children of mothers who reported severe symptoms either early or later in the postpartum period were more likely to show impaired growth at 18 and 36 months postpartum. In this case, findings suggest that, even if transient, severe depressive symptoms during the postpartum period can have adverse effects on child growth. These findings also indicate that the timing of severe symptoms may be less important that suggested in previous literature (Kingston *et al.*, 2012, Stein *et al.*, 2014).

The only qualitative difference in child development found between the *early* and *late postpartum* trajectories was that greater peer problems were reported among children of mothers belonging to the *late postpartum* trajectory. No other differences were found in terms of cognitive, socio-emotional

and behavioural development at 18 or 36 months postpartum. This is surprising, given the developmental pathways between antenatal or postnatal depression and child development proposed in the literature (Herba *et al.*, 2016). Indeed, evidence suggests that depressed mothers are less responsive and sensitive to their child's needs, less facial and vocally expressive, tend to have harsher contact with their infant and exude negative affect - all of which impact on whether and how children's attention is solicited (Sohr-Preston and Scaramella, 2006). In the first three months postpartum, such behaviours impact infants' ability to develop associative learning and symbolic thought – both of which are essential cognitive milestones. However, it is only later in the postpartum period that infants' ability to communicate develops drastically, where joint attention and pretend play are important activities which enhance children's language development and interaction skills. These can also be affected by depressed mothers' behaviours, however, and delays in these skills can have repercussions on the child's ability to communicate effectively during the toddler years (Sohr-Preston and Scaramella, 2006). This may explain the peer-related problems identified among children of mothers reporting severe symptoms later, rather than earlier, in the postpartum period.

It is surprising that no associations were found between the *chronic high* trajectory and child development, besides lower scores on the emotional subscale of the Strength and Difficulty Questionnaire (SDQ) at 36 months postpartum. Given the poorer growth outcomes reported among children of mothers with severe symptoms in the postpartum period, one would expect that women reporting severe symptoms both antenatally and postnatally would have children reporting similar growth impairment, if not worse. Indeed, there is evidence suggesting that, even antenatally, depression can lead to undernutrition and poor self-care, which in turn can lead to poor foetal development, a precursor to poor child growth (Grote *et al.*, 2010, Parsons *et al.*, 2012, Herba *et al.*, 2016). The present findings are likely related to the *chronic high* trajectory's small sample; a bigger sample may have been better powered to identify differences in child development among children of mother belonging to this trajectory.

Unfortunately, Barthel *et al.* (2017) did not investigate child development in their study of trajectories of perinatal depressive symptoms in West Africa, so it is not possible to compare the above results with another study from a LMICs. However, a recent systematic review, published simultaneously with the systematic review presented in Chapter 2, reviewed studies investigating the heterogeneity of perinatal or maternal depressive symptoms, this time assessing differences in child outcomes (Santos *et al.*, 2017). Studies included in the review did not necessarily use GCMM, but any statistical method that allowed for latent clusters or groups to be generated using longitudinal data. Nine studies included in Santos *et al.* (2017)'s review reported on child outcomes, and only one was conducted in

an LMIC and reported on maternal depressive symptoms until six years postpartum among a Brazilian sample. On the whole, the review indicated that worse health or development outcomes were reported for children of mothers assigned to more severe depressive symptom trajectories – whether severe symptoms were transient or chronic; these findings support those reported in Chapter 4.

Indeed, studies included in the review which reported both chronic and transient trajectories indicated greater internalising symptoms, and more problems with executive function and memory among seven- to eight-year-old children of mothers with heterogeneously high symptom levels from pregnancy to 12 months postpartum (Vänskä *et al.*, 2011), as well as worse socio-emotional and behavioural problems among five-year-old children of mothers with persistently severe depressive symptoms from birth to five years postpartum (van der Waerden *et al.*, 2015). However, in both studies, children of mothers with transient severe symptoms in the early postpartum period (Vänskä *et al.*, 2011) and pre-school years (van der Waerden *et al.*, 2015) also reported internalising problems and socio-emotional and behavioural problems, respectively. This was supported by a recent study conducted in Canada (Kingston *et al.*, 2018), not included in Santos *et al.* (2017)'s review. In this study, children of mothers belonging to all higher risk trajectories ('persistently high', 'early postpartum' and 'subclinical') showed worse hyperactivity/inattention and physical aggression and worse separation anxiety compared to children of mothers with low levels of depressive symptoms. However, studies included in Santos' review which reported relatively chronic trajectories, characterised by different levels of severity, seem to suggest that depressive symptoms, even if mild, may also play a role in predicting poorer child outcomes. For example, Cents *et al.* (2013) found internalising and externalising problems among children of Dutch mothers with chronic mild, moderate and severe trajectories. Similarly, worse emotional behavioural functioning was found among children of mothers with subclinical and severe persistent depressive symptoms in an Australian study, compared to mothers with minimal depressive symptoms (Giallo *et al.*, 2015a). Further research with bigger samples is therefore required to clarify the findings reported in this thesis, and to determine whether the effects of depressive symptoms on child growth and development may be different when these are chronic, in addition to severe.

The results reported in Chapter 4 are particularly noteworthy given Rotheram-Fuller *et al.* (2018)'s concurrent study, conducted among both arms of the Philani cluster randomised controlled trial (RCT) described in Chapter 4. Women were allocated to predefined groups based on the number of times they scored 13 or above on the Edinburgh Postnatal Depression Scale (EPDS), the validated cut-off in South Africa (Rochat *et al.*, 2013b), from pregnancy to 5 years postpartum: never, antenatal only, postnatal only, and antenatal and postnatal. They then compared child growth and development at

18 and 36 months across groups. Similarly to findings reported in Chapter 4, they also found no differences in executive function but differences in growth outcomes across severity groups. However, they report greater internalising and externalising problems, measured on the Child Behaviour Checklist, among children of mothers who screened positive at any point in the postpartum period, regardless of their symptom levels during pregnancy. Socio-emotional and behavioural problems, measured on the SDQ, were also greater among children of mothers who screened positive at any point during the pregnancy and the postpartum period. The different results from Chapter 4 may be due to the inclusion of the intervention arm in Rotheram-Fuller *et al.* (2018)'s study. Indeed, they explain that the Philani intervention did not have any impact on depressive symptoms, which is the reason why both arms were combined in their study. However, some differences in child growth, in mothers' breastfeeding duration and prevention of HIV transmission were found between depressed mothers receiving the intervention compared to depressed mothers in the control group (le Roux *et al.*, 2013, Tomlinson *et al.*, 2015a, Tomlinson *et al.*, 2016). For this reason, it is unclear whether similar results would have been found among the control group only in Chapter 4, had child development outcomes been compared across the same pre-defined categories. It is worth noting that the premise of GCMM is that it provides a more nuanced and transparent picture of the course of depressive symptoms over time. This is certainly useful for research and clinical purposes, as it helps gain a better understanding of the aetiology and prognosis of perinatal depression. However, it may be less useful in understanding the relationship between perinatal depression and child development: it may be that pre-defined groups and identifying women who screen positive on a screening instrument may be enough to identify children at risk for developmental problems. Future research should investigate child development in relation to trajectories of perinatal depressive symptoms using both methods, within the same sample, and assess whether different conclusions can be drawn.

6.1.4. Perinatal depressive symptoms and suicidal risk

Having established that the course of perinatal depressive symptoms does vary across women, and that such variations can be predicted by different risk factors and have different consequences on child growth and development, it seems important to assess how the course of suicidal behaviours relates to the course of depressive symptoms, since both have been intrinsically linked in perinatal mental health literature. The results reported in Chapter 5 indicate that, among women initially at risk for depression, depressive symptoms were associated with severity of suicidal risk, but only when depressive symptom levels decreased, and this was only the case among women younger than 36 and who belonged to the *antenatal only* trajectory. In other words, any worsening in depressive symptom levels did not translate into an increase in severity of suicidal risk, and any decrease in depressive

symptom level did not translate into a decrease in suicidal risk across all perinatal women – an assumption which is repeatedly made by including a suicide item in screening instruments for depression. For this reason, it may be preferable to consider both entities as overlapping but relatively independent for both research and clinical purposes.

The fact that a reduction in the severity of depressive symptoms was not associated with a decrease in severity of suicidal risk among women who presented with an *antenatal and postnatal* depressive symptom course could reflect the presence of social and economic contextual influences which led to both symptoms of depression and increased suicidal risk. Indeed, results from Chapter 3 indicated that women belonging to this trajectory were at higher risk of experiencing multiple social, economic and health stressors compared to women who showed a relatively natural remission. In this case, results could suggest that women were at risk for suicide, regardless of their level of depressive symptoms, as both were a consequence of adverse contextual influences, rather than suicidal risk being a consequence of depression severity per se. Further research is required to investigate this possibility.

Taking one step further, results could suggest that the relationship between the course of perinatal depressive symptoms and suicidal risk may differ according to women's depression profile. Indeed, in a recent study conducted by the Postpartum Depression: Action Towards Causes and Treatment (PACT) consortium, secondary data analyses were conducted on data and records collected in seven different countries (US, Australia, France, Sweden, The Netherlands, Denmark and the UK) to identify different subtypes of postnatal depression, based on time of onset, severity of symptoms and item responses on the EPDS, using latent class analysis (Putnam *et al.*, 2015). They report three different subtypes of depression, each of which were associated with different severity of symptoms, timing of onset, perinatal complications, history of mood disorder, and degree of comorbid anxiety and suicidal ideation. A different pattern of association between depressive symptoms and severity of suicidal risk may therefore have been identified among women with little or no initial depressive symptoms during pregnancy, a group which was excluded from the study. The possibility of trajectories reflecting different symptom profiles is discussed in more detail later in this Chapter.

6.2. Limitations

There are several limitations that should be borne in mind when interpreting the results presented above. These include the fact that i) the findings may not be generalisable to other populations; ii) findings from Chapters 2 to 5 were based on secondary data analyses; iii) assessments of depressive

symptoms were wide apart and not assessed before pregnancy; iv) screening instruments were used to measure depressive symptoms; and v) the heterogeneity of depressive symptom profiles was not assessed. Each of these limitations are discussed in more detail below and are considered in the context of broader issues and debates in the field of global mental health and perinatal mental health.

First, studies reported in Chapter 3 to 5 were conducted in Khayelitsha, and while this setting resembles many township settlements in South Africa (Housing Development Agency, 2012), the findings reported may not be generalisable to other low-income settings in South Africa or other African countries. Also, it must be noted that the original studies used were RCTs, and so the randomisation and receipt of interventions, even if non-effective, may have led to changes in the characteristics of this sample – characteristics which may have differed from those of a descriptive cohort sample.

Second, more generally, the use of secondary data means that analyses and interpretations were bound to the original studies' sample sizes and inclusion criteria, as well as to the studies' design, including the number of assessments conducted, time elapsed between assessments, and the content of the questionnaires administered at each assessment. In Chapter 4, an attempt was made to address the limitations of the analysis reported in Chapter 3, namely the potential effect of the enhanced usual care provided to participants allocated to the control arm and the relatively small sample size. However, in both Chapters 3 and 4, assessments remained wide apart, when ideally assessments should be conducted on a monthly basis to be able to generate more accurate latent trajectories of depressive symptoms over time. In Chapter 4, I refer to one of the trajectories as *chronic high*, admittedly a loose description. Several definitions have been used in the literature to describe chronic depression: some define it as continuous or recurrent symptoms (without full remission) for at least six months (Campbell and Cohn, 1999, Kurstjens and Wolke, 2001), while for others, symptoms must have been present for 24 months to be considered chronic (Appelbaum *et al.*, 1999), including in the DSM-V classification (McCullough Jr *et al.*, 2003). However, in Chapters 3 and 4 the first and last assessments were, on average, 15 and 21 months apart, respectively, falling short of the two-year mark. It is also possible that participants belonging to the high-risk trajectories recovered fully from their symptoms between two assessments. Wide intervals mean that one runs the risk of reporting what seems like chronically elevated depressive symptoms, when in fact such levels of symptoms may be episodic. The risk profiles and impact on the mothers' health and child development may be very different for those who present episodic versus chronic depressive symptoms.

Third, there were no assessments of symptoms just before pregnancy, even retrospectively. With longitudinal studies, one runs the risk of assuming that depressive symptoms reported at the first assessment in the perinatal period is the first episode of depression. Yet, there is growing evidence suggesting that this represents a minority of women suffering from perinatal depression. One study in the United States investigated the onset of symptoms using retrospective self-report among women diagnosed with depression at three to five weeks postpartum (Fisher *et al.*, 2016). They found that a quarter of the women reported onset before pregnancy, 37% reported onset during pregnancy, and 38% in the postpartum period. Another longitudinal study conducted in Italy followed women up from the third trimester of pregnancy to 12 months postpartum (Banti *et al.*, 2011). Results indicated that the majority of women diagnosed during pregnancy were already depressed just before pregnancy: 8.6% were found to be depressed at the first assessment, but this was a first onset for only 1.6% of the women. Very few new cases of depression were also reported in another longitudinal study in Germany, where women were followed-up from the first trimester of pregnancy to 16 months postpartum (Martini *et al.*, 2015). Authors reported that 23% of women who were depressed before pregnancy were depressed at some point during pregnancy or the postpartum period, and that the cumulative incidence of depression during pregnancy and the postpartum period was only 2.5% and 7.5%, respectively. In Chapter 3, results indicated that a past diagnosis of depression at any point was associated with greater odds of women belonging to the more severe *antenatal and postnatal* trajectory. So, it is possible that women allocated to this trajectory already suffered from depression before pregnancy.

This evidence points to the idea that perinatal depression can be a continuation of pre-existing symptoms, as mentioned in Woody *et al.* (2017)'s global review of the prevalence and incidence of perinatal depression. In their review, they question whether, given the age group, women could have become depressed even without getting pregnant. Whether perinatal depression is just an episode of depression that occurs during the perinatal period, or whether perinatal depression is a different and distinct disorder in its own right has been the subject of debate in the field (Wisner *et al.*, 2013, Putnam *et al.*, 2015). For public health purposes, this may be less important to disentangle, given that the impact on functioning and health are just as important, if not more, given the implications on child development. In the present study, however, the trajectories may be confounded by the women's history of depression, in that women with and without a history of depression may show a different pattern of symptom change over time when they become pregnant or give birth. Indeed, pregnancy and motherhood is often viewed as a trigger for depression – one of the reasons why some argue that perinatal depression is biologically different from depression in the general population (Department of Health, 2012). Future studies on trajectories should consider including an assessment of history of

depression, and consider whether symptoms which are present during pregnancy began pre-pregnancy. This would shed light on whether the course of perinatal depressive symptoms differs depending on the women's history of depression, but may also have implications on which treatment approach should be taken, since depression which was present before pregnancy implies a form of depression that is not related to hormonal change or stress related to pregnancy or motherhood-related demands (Fisher *et al.*, 2016).

A fourth limitation relates to the use of screening instruments to measure depressive symptoms, which is inevitable in GCMM where the use of a continuous measure is required. Indeed, despite screening instruments being developed and their validity assessed in relation to a gold standard – most often a diagnostic assessment based on either ICD or DSM criteria – some limitations to the use of the EPDS and Hamilton Depression Rating Scale (HDRS) remain. For one, neither the EPDS nor the HDRS include an item on functioning, even though this is one of the key criteria for a diagnosis of depression. It is perhaps not a coincidence that functioning was one of the most important risk factors identified for the *antenatal and postnatal* trajectory in Chapter 3. A measurement of functioning could be crucial in determining women at risk for depression by differentiating those who suffer from distress from those suffering from moderate or severe depressive symptoms which are debilitating and impair women's functioning. A functioning item was included in a recently developed short screening tool to assess 'how bothered' pregnant English-speaking women were by each symptom of depression and anxiety they reported (Matthey and Agostini, 2017). Validation studies so far have shown that this screening tool performed better at detecting depression than the EPDS, Hospital Anxiety and Depression Scale or the PHQ-9 (Matthey *et al.*, 2013, Matthey and Bilbao, 2018), all instruments commonly used to screen for perinatal depression.

Also, many of the symptoms experienced during pregnancy or early postpartum period could be mistaken for somatic symptoms of depression assessed in the HDRS. For example, in a study by Matthey and Ross-Hamid (2011) conducted in Australia, women in their second or third trimester of pregnancy were interviewed using the MINI Depression module and asked, for each symptom presented, whether they thought the symptom was due to pregnancy's physical changes or their mood. Results indicated that 66% of women who originally met criteria for depression no longer did once all pregnancy-related symptoms were taken into account. This limitation does not apply to the EPDS, which was specifically developed to overcome this issue and therefore excludes any somatic symptoms likely to occur during pregnancy or in the early postpartum period (Matthey and Agostini, 2017). It is probably for this reason that the EPDS is the most commonly used screening tool for perinatal depression worldwide (Woody *et al.*, 2017), and is the reason why this instrument was used

to identify women at risk for depression in Chapter 3, and to measure change in depressive symptoms in Chapter 4.

Other limitations have been reported with the use of the EPDS, however. For one, several items, such as the item "Things have been getting on top of me", have repeatedly been reported as ambiguous and misunderstood (Matthey and Agostini, 2017). The anxiety-related items have also been shown to exclude individuals with high levels of stress, since the item specifies "for no good reason". Finally, the self-harm related item is sometimes misinterpreted as referring to accidental harm (Kim *et al.*, 2015, Matthey and Agostini, 2017), which has direct implications on the use of the item as a measure of suicidal risk, often the case in research on suicidal risk among perinatal women in South Africa (Cooper *et al.*, 1999, Dewing *et al.*, 2013, Rochat *et al.*, 2013a). The extensive adaptation and validation of the isiXhosa version of the EPDS (De Bruin *et al.*, 2004), used for both Chapters 3 and 4 may, however, have overcome some of these misinterpretations. Second, the recall period on the EPDS is only one week, whereas both ICD-11 and DSM-V classification specify that symptoms must have been present for at least two weeks to quality for an episode of depression. Such a short recall period can lead to measuring transient symptoms of distress, which can be especially problematic during pregnancy, when women may experience short-term pregnancy-related stressors as they adapt to their new situation. A study by Matthey and Ross-Hamid (2011) administered the EPDS twice to pregnant women in Australia with a two-week interval. Results indicated that half of the participants no longer screened positive. Authors also found that the majority of women correctly predicted that they would feel better by the time of the second assessment, as most of the stressors were pregnancy-related and time-limited, such as nausea or fear of miscarriage. The applicability of Matthey and Ross-Hamid (2011)'s findings may be questionable in LMICs, however, where pregnant women may experience societal and economic stressors which are more endogenous and chronic than those faced by women living in HICs.

More generally, some researchers question the validity of depressive symptoms assessed in screening instruments, which are validated against criteria that are relevant to Western populations, but not necessarily relevant to other populations in LMICs (Matthey and Agostini, 2017). For example, results from a recent systematic review of qualitative studies in non-Western countries (Haroz *et al.*, 2017) indicated that three of the most common features reported were included as core criteria for a depression diagnosis in the DSM-V classification: depressed mood/sadness, fatigue or loss of energy, and problem with sleep. However, many features that were reported were also not part of the current classification, such as worry, issues with breathing, irritability and problem with sleep or restlessness. Among perinatal women specifically, the most common features reported were social isolation or

loneliness, depressed mood/sadness and fatigue or loss of energy; the first feature not being a criterion for depression according to DSM-V. The different features identified for depressive symptoms within and across regions and cultures lead to question the validity of the DSM-V criteria for depression among non-Western populations (Matthey and Agostini, 2017), and highlight the possibility that screening instruments used to measure symptoms of depression, such as the EPDS and HDRS, may not be comprehensive or reflective of how individuals experience depression in LMICs.

However, a somewhat different finding was reported in a formative qualitative study conducted in Khayelitsha in preparation for the AFFIRM trial. This study explored the experiences and views of pregnant women on depression. Both depressed and non-depressed women, based on the MINI diagnostic assessment, were interviewed and their experiences compared to the ICD-10 and DSM-V classifications (Davies *et al.*, 2016). Authors reported that the majority of the symptoms of depression described were consistent with diagnostic classifications, however the way in which they were described varied as women relied mostly on local idioms. Women also reported fear and anxiety, stress headaches, body pains and anger as symptoms of depression. These are not listed as key symptoms in the DSM or ICD classifications of depression, however they are indicated as "Associated features supporting diagnosis" or included under the criteria for "MDE with anxious distress" in the DSM-V (American Psychiatric Association, 2013). This study therefore suggests that the depressive symptoms measured with the EPDS and the HDRS may be relevant to the perinatal women living in Khayelitsha all the same. Given the limitations of screening instruments highlighted above - the lack of functioning item, the inclusion of somatic symptoms in the HDRS, as well as the misinterpretation of key items and short recall period of the EPDS, the trajectories reported in Chapters 2 to 4 should nonetheless be interpreted with caution.

A final limitation to the study was the fact that types of symptoms reported, or symptom profiles, were not investigated as predictors of specific trajectories identified in Chapters 3 and 4; this was beyond the scope of the present thesis. Similarly, none of the studies included in the systematic review reported in Chapter 2 investigated symptom profiles as predictors of specific trajectories generated though GCMM. And yet, trajectories could in fact reflect a single trajectory for different subtypes of depression. Indeed, heterogeneous profiles of symptoms have been reported in the literature and are seen in practice (Nandi *et al.*, 2009). For example, in a second, more recent study conducted by the PACT consortium, using data sources for all seven countries (US, Australia, France, Sweden, The Netherlands, Denmark and the UK), different subtypes of postnatal depression were identified based on time of onset, severity of symptoms and scores on three different constructs on the EPDS: anhedonia, depressed mood and anxiety (Putnam *et al.*, 2017). With the use of principal components

and common factor analyses, they identified five subtypes of depression: moderate or severe anxious depression, anxious anhedonia, pure anhedonia and resolved depression – all differed in terms of onset, severity of symptoms and endorsement of anxiety and self-harm items. Nandi *et al.* (2009) conducted a systematic review on the heterogeneity of common mood and anxiety disorders among the general population. All but one study, of the nine relevant studies in the review, reported at least five different subtypes of depression or 'syndromes' – some differed only in terms of severity, but most differed in their presentation of specific symptoms. The most commonly reported subtype of depression across studies was the 'atypical depression' subtype, characterised by anhedonia, sleep or eating disturbances and greater chronicity of symptoms.

The subtypes of depression identified in Nandi *et al.* (2009)'s systematic review only included studies from HIC, and so may not be relevant to the South African setting. Nonetheless, it is possible that the heterogenous trajectories identified in this thesis may in fact be the product of heterogeneous subtypes of depression, each characterised by a different trajectory. Thus, future studies assessing the heterogeneity of trajectories of perinatal depressive symptoms in LMICs should investigate this possibility further, as this would have important implications for both research and practice.

6.3. Recommendations for future research

Bearing in mind the limitations discussed above, the study establishes a strong basis to develop further evidence on the course of perinatal depressive symptoms in LMICs and their association with risk factors, child outcomes and suicidal risk over time (see Box 6.1). The use of GCMM to investigate latent trajectories of depressive symptoms among perinatal women overcomes many of the limitations of common methods of analyses and designs usually employed in this field, including cross-sectional studies, single growth longitudinal studies and studies using pre-defined chronicity and severity groups based on screening instruments cut-off scores. Indeed, GCMM offers a less variable-oriented method of creating latent groups of women with similar trajectories of symptoms over time, and circumvents the need to dichotomise symptom severity. However, additional evidence using GCMM with more assessments, including an assessment of symptoms before pregnancy, and shorter intervals is needed, especially given the episodic nature of depression. It is also essential that the instruments used to assess symptoms of depression be valid among the study populations, given the limitations of DSM-V and ICD-11's validity in non-Western populations. Future research should also investigate the role of food insecurity, rather than socio-economic status or wealth, in predicting trajectories, the latter often being reported but not valuable in differentiating women with higher risk trajectories from those with low or transient symptoms during the perinatal period. The current literature on the

heterogeneity of depression symptom profiles show how vital it is to also consider differences in types of symptoms presented across the different trajectories. This would go a long way in gaining a better understanding of the aetiology of perinatal depression and in developing targeted preventive interventions.

Box 6.1. Recommendations for future research on trajectories of perinatal depressive symptoms in LMICs

- Future studies employing growth curve mixture modelling methods should:
  - Recruit bigger samples to allow smaller but clinically valid trajectories to be identified
  - Include more assessments of depressive symptoms, with shorter intervals
  - Use valid measures of depressive symptoms for the population under study
  - Investigate the role of food insecurity further in differentiating higher-risk trajectories from low-risk ones
  - Investigate the role of depressive symptom profiles in relation to symptom trajectories
- The presence of different trajectories of perinatal depressive symptoms should be taken into account in the design or analysis of randomised controlled trials assessing the effectiveness of interventions for depression
- Growth curve mixture and mixed effects modelling should be used to identify mediators and moderators of the pathways between psychosocial risk factors and trajectories of perinatal depressive symptoms, and between trajectories and child outcomes.
- The role of anxiety and depression on child outcomes should be investigated

Findings from the present study also have implications on how to assess the effectiveness of interventions for perinatal depression. First, results from Chapter 5 clearly suggest that interventions for perinatal depression should include independent and separate assessments of depressive symptoms and suicidal risk. Second, researchers are likely to underestimate or overestimate the effect of an intervention if they ignore the presence of different trajectories of depressive symptoms over the perinatal period. Two different methods have been suggested as a way for researchers to take

different trajectories among samples into account and differentiate these from the effects of the intervention. This can be done at the analysis stage by including the arm variable in the longitudinal model, so that trajectories are generated per arm (Muthén *et al.*, 2002, Leiby, 2012); or a normal model can be run and then the trajectory membership cross-tabbed with the arm variable. In both cases, post-hoc analyses would investigate the baseline differences that could explain the different trajectories according to arm or identify the characteristics of those individuals most likely to improve or respond to the intervention. Taking one step further, Muthén and Brown (2009) argue that, given different trajectories, participants have a predisposition to respond to control or treatment interventions even before the randomisation takes place. By using specific methods within GCMM, they explain that researchers can allocate participants to different subgroups in RCTs: treatment or control responders only, never responders or always responders. Such methods can make important advances in how researchers approach the comparison of control and treatment interventions in RCTs.

It was not possible in Chapter 4 to differentiate the role of chronicity versus severity of perinatal depressive symptoms on child development. This is partly due to the relatively small sample in the *chronic high* trajectory. For this reason, it is essential that future studies in LMICs be better powered, with bigger samples. One assessment of child outcome measures is also not sufficient (Sutter-Dallay *et al.*, 2011, Giallo *et al.*, 2015a): longitudinal assessment of child outcomes would allow researchers to get a better understanding of the association between perinatal depressive symptoms and child development over time. Such associations have often been reported as bidirectional, with children's behaviour and development also affecting mothers' symptoms – what is also known as the transactional effect (Goodman *et al.*, 2011, Stein *et al.*, 2014, Liu *et al.*, 2017). With these considerations in mind, researchers will be better placed to identify whether transient severe symptoms or chronic symptoms, regardless of severity, have qualitatively different consequences on child development.

It was beyond the scope of the present study to assess mediators and moderators of perinatal depressive symptoms on child development. Only known confounders – age, education and wealth status – were included in the analyses in Chapter 4. This was necessary as socio-economic characteristics tend to reflect the adverse context in which children are growing up and the stressors that could contribute to their development of psychopathology (Goodman *et al.*, 2011). However, as seen in Chapters 3 and 4, social and economic factors in LMICs are also associated with perinatal depression. Thus, these factors could represent moderators or mediators of the effects of perinatal depression on child outcomes rather than confounders as such. Future studies making use of GCMM should therefore investigate this further, as child development is likely to be the result of a complex

interaction of individual (biological, psychological) and social risk factors, all of which are broadly influenced by greater community and structural societal factors, such as poverty and cultural norms (Stein *et al.*, 2014, Liu *et al.*, 2017). For example, the mother's sensitivity and responsiveness to her child have been shown to mediate the relationship between maternal depression and child outcomes. Evidence from LMICs also indicates that women suffering from perinatal depression have more difficulty forming a bond and secure attachment with their child, and this is turn leads to impaired child emotional and cognitive development (Parsons *et al.*, 2012); findings which have been supported by extensive work conducted by Cooper and colleagues in Khayelitsha (Cooper *et al.*, 1999, Tomlinson *et al.*, 2005, Cooper *et al.*, 2009). Finally, social factors, such as marital difficulty and family conflicts have also been suggested as mediators between improved perinatal depressive symptoms after a parenting intervention and improvements in child outcomes (Goodman and Gotlib, 1999).

GCMM is informative in identifying different growth curves among the same population and in identifying high-risk groups of women who may show different trajectories over the perinatal period and who may need to be targeted for interventions. This method is less intuitive, however, when it comes to making inferences on the causal pathway between socio-economic, health and psychosocial factors and specific growth curves. This was beyond the scope of this thesis, but future studies could employ mixed effects methods to identify mediators and moderators of rate and direction of change in symptoms over time. Such mediators could be personality and physical health, which have been shown to affect how psychosocial and economic adversity impact on perinatal depression. For example, in a longitudinal study in Khayelitsha, personality traits mediated the association between food insecurity and high level of depressive symptoms among pregnant women (Tsai *et al.*, 2012). In the same study, social support also mediated the link between food insecurity and depressive symptoms: food insecurity predicted high risk for depression one year later, but this effect was buffered when social support was taken into account, particularly instrumental support. Identifying mediators and moderators of perinatal depression would ultimately help inform which elements to include in psychosocial interventions. Indeed, in the context of economic and social adverse circumstances, which often cannot be addressed at the individual level, addressing these factors to help strengthen resilience should contribute towards reducing depressive symptoms and promote mental health. Doing so enables such interventions to address both depressive symptoms and circumstances which are intrinsically linked to their mental wellbeing, acknowledges the social determinants of mental health and contributes to reducing the stigma associated with receiving mental health care. Also, this addresses some concerns that purely psychological treatments may be too complex and not adapt well to brief interventions (Mathieson *et al.*, 2009), which in LMICs, are essential for task-sharing purposes.

Though limited, there is growing evidence of the use of GCMM to identify trajectories of anxiety symptoms among perinatal women (Barthel *et al.*, 2016, Lim *et al.*, 2018). This is warranted given how prevalent anxiety is among this population. Indeed, evidence suggests that anxiety may be even more prevalent than depression during this period (Lee *et al.*, 2007, Martini *et al.*, 2015). In South Africa, 15.2% of pregnant women living in an urban area of Soweto were at high risk for anxiety (Redinger *et al.*, 2017), while 7.3% were at high risk for depression and anxiety. This reflects findings from a recent systematic review suggesting anxiety and depression were highly comorbid during pregnancy (Biaggi *et al.*, 2016). Barthel *et al.* (2017)'s study also found that the trajectories of depressive symptoms among women in West Africa were highly associated with trajectories of anxiety symptoms from pregnancy to two years postpartum. Finally, there is growing evidence that stress during pregnancy has adverse effects on foetal development and on infant development after birth (Stein *et al.*, 2014, Surkan *et al.*, 2016). Lim *et al.* (2018) used group-based modelling to assess the trajectories of stress and anxiety among Singaporean pregnant women. They found that women allocated to the trajectory characterised by chronically severe stress had greater risk of having low-birth weight babies and babies with smaller head circumference. Further research should therefore investigate the effect of trajectories of anxiety symptoms on child outcomes and investigate whether these are qualitatively different from the effects of chronic or severe symptoms of depression, or different from the effects of comorbid depressive and anxiety symptoms. For example, some preliminary evidence from a longitudinal study suggest that low positive affect (depression) may be more detrimental to children's emotional negativity than is high negative affect (anxiety) (Prenoveau *et al.*, 2017).

6.4. Recommendations for perinatal mental health services in South Africa

The findings reported in this thesis make an important contribution to the literature on the different trajectories of perinatal depressive symptoms in low-income South African settings, how these are associated with suicidal risk over time, how trajectories can be predicted so that women with more severe and chronic symptoms can be identified, as well as how these impact on child outcomes. Such findings have direct implications on the mental health service needs of low-income perinatal women in South Africa, and implications on the identification and prevention strategies that need to be put in place to reduce the burden of perinatal depression (see Box 6.2). These are discussed in more detail below, and suggestions on how these could be implemented are provided given the South African health system context.

6.4.1. Identification and management of women at risk for perinatal depression

The present findings suggest that any identification mechanism for women at risk for perinatal depression should be a continuous process and conducted throughout the perinatal period. It is difficult to say from results in Chapter 2 to 4 when such identification assessments should ideally take place, given the timing of assessments were inconsistent across studies. It does seem that symptoms which remain elevated just before birth are likely to remain elevated or worsen in the postpartum period, and women whose symptoms remit naturally will have seen their symptoms decrease by the end of pregnancy. Therefore, assessments should ideally be conducted at women's first antenatal visit, as well as in the third trimester. Given the high-risk and *early* or *late postpartum* trajectories reported in Chapters 2 and 4, assessments should also be conducted at two, six months and 12 months postpartum at the very least.

Second, such assessments should not only include measurement of depressive symptoms, but also of suicidal risk, and this independently from one another. Also, identifying perinatal women at risk for depression or suicide cannot be complete without integrating a simultaneous assessment and monitoring of contextual stressors, such as the presence of adverse health, social and economic-related circumstances. Given results from Chapter 3 and 4, assessing social support and alcohol use during pregnancy may be particularly useful in identifying women who are at higher risk of reporting severe and chronic depressive symptoms during the perinatal period, rather than symptoms which decline naturally. Assessing the presence of multiple stressors will also help in identifying women whose severity of suicidal risk may not abate as symptoms of depression decline over the course of the perinatal period. It is also essential to continue to monitor symptoms for both perinatal depression and suicidal risk, even when women show signs of remission or stable subclinical levels of depression, such as for the *antenatal and postnatal* trajectory in Chapter 3, or the *early* and *late postpartum* trajectories in Chapter 4.

The inclusion of the three-item mental health screening tool in the maternity case records in the Western Cape (Appendix A), which is likely to be scaled up nationally, is a promising development in the identification of pregnant women at risk for depression or suicide. As explained in Chapter 5, the three items are to be asked at each antenatal visit and pertain to low or depressed mood and thinking too much – the former being one of the three most commonly reported symptoms among pregnant women in non-Western countries (Haroz *et al.*, 2017). 'Thinking too much' was also one of the most common idioms of distress reported by pregnant women in Khayelitsha in a study conducted as part

of the AFFIRM trial's formative phase (Davies *et al.*, 2016). The fact that the assessment of suicidal risk is independent from that of the mood-related questions is also a step in the right direction.

Box 6.2. Recommendations for the identification and referral of women suffering from perinatal depressive symptoms

- Separate the identification of perinatal women at risk for depression and suicide
- Identify and monitor women at risk for depression and suicide throughout the perinatal period
- Assess psychosocial and economic contextual factors in addition to depressive symptoms, including alcohol use during pregnancy and level of social support
- Refer women to different types of treatment depending on severity of symptoms and likelihood of these being chronic
- Include education on maternal behaviours and alcohol use during pregnancy
- Monitor child growth postnatally if women report severe depressive symptoms
- Include feeding practices and parenting elements in psychosocial interventions for perinatal depression to promote child growth and development

Some limitations to the use of this three-item mental health screening tool remain, however, such as the fact that it does not take women's psychosocial and economic contextual stressors into account, nor does it include an assessment of functioning. The need to take contextual factors into consideration when assessing women's risk for perinatal depression has been acknowledged by the Perinatal Mental Health Project, an organisation providing counselling during pregnancy and the postpartum period to women attending one of three Midwife Obstetrics Units (MOU) in the Cape Town area. They offer routine screening to all women attending the MOUs using the EPDS and a screening tool they refer to as the Risk Factor Assessment (RFA), an 11-item instrument listing a range of factors known to affect perinatal depressive symptoms, such as lack of partner or family support, unwanted pregnancy, previous pregnancy or child loss and history of depression or other mental illness (Honikman *et al.*, 2012). Authors explain that any woman who endorses three or more risk factors is offered counselling, regardless of the presence of depressive symptoms. Unfortunately, the validity of this instrument remains to be assessed.

6.4.2. Referral mechanisms

A clear referral pathway would have to be put in place for women who are identified as being at risk for perinatal depression or suicide, or who are likely to be suffering from chronic severe perinatal depressive symptoms. In light of the present findings and given the limited resources available for perinatal mental health care, referrals and treatment could focus on the more at-risk perinatal population, such as women who are likely to suffer from severe and chronic depressive symptoms throughout the perinatal period – a group which can be identified during pregnancy already. However, there is evidence that even milder depressive symptoms can have debilitating effects on distress, functioning and need for care (McGorry and Nelson, 2016), and that individuals who suffer from mild or moderate depressive symptoms make up the majority of the disability burden associated with depression (Judd *et al.*, 2000, Patel, 2017). Also, findings in Chapter 4 indicate that, even if not chronic, severe depressive symptoms can have adverse effects on child physical growth.

For this reason, a stepped approach could be taken, where on the one hand, women with milder depressive symptoms could be referred to community-based interventions, such as peer support groups, or NGOs addressing issues of alcohol use, or IPV, and on the other hand, women who suffer from more severe or chronic symptoms would be referred for more intensive psychological intervention, or for medication, which is sometimes a preferable course of treatment compared to no treatment at all (Kennedy, 2013, Myles *et al.*, 2013). This goes in line with the South African National Mental Health Policy and Strategic Plan (Department of Health, 2013), which recognises the importance of NGOs and other organisations in the provision of mental health, and promotes community, peer and family-supported task-sharing for mental health care (Eaton *et al.*, 2011).

This type of stepped care strategy was also proposed in the staged model (McGorry and Nelson, 2016, Patel, 2017). According to this model, and by taking into account transdiagnostic symptoms, contextual circumstances and functional impairment, women with mild or moderate symptoms of depression would be recategorised as reporting distress (e.g. mixture of anxiety, mood and somatic symptoms) and referred to community level support groups or peer support groups, while those reporting severe depressive symptoms with functional impairment in social life would be recategorised as suffering from a depressive disorder and would receive psychosocial and/or medication at health system level. This model views depression as dimensional, however, which allows variations in terms of profiles of symptoms, severity and chronicity, each with specific developmental pathways and responses to different treatments (Mulder, 2005, Cuijpers, 2014, Thangadurai and Jacob, 2014). A dimensional view of depression is likely to be more accurate from an

epidemiological standpoint, but it is often less practical for practitioners, who prefer the use of binary classifications, such as with screening instruments, as they facilitate identification, referral and treatment decisions (Jacob and Patel, 2014, Patel, 2017). The staging model, however, approaches the identification and management of mental illness in such a way that combines a dimensional view of mental disorders but still enables feasible identification for primary healthcare workers. Whether this is a feasible option in South Africa is still to be determined, however.

6.4.3. Preventing adverse child outcomes

Psycho-education on the effects of maternal behaviour on the foetus, including alcohol use, should also be provided during pregnancy. This is the kind of intervention that is already provided by Philani, an NGO based in 150 township settlement neighbourhoods, which was initiated specifically to improve children's nutritional status. The peer support and counselling intervention, consisting of four sessions during pregnancy and four sessions after birth and provided by peer community health workers (CHW), focuses on HIV, nutrition and alcohol use in order to improve mothers' health care utilisation, HIV-related preventive behaviour, social support and mental health, as well as their children's growth and health (Rotheram-Borus *et al.*, 2011). There is evidence that the intervention is effective in reducing the proportion of infants with low birthweight, in improving weight-for-age z-scores at 18 months postpartum and in increasing the duration of exclusive breastfeeding, but not in improving maternal depressive symptoms. However, preliminary findings from a pilot study conducted in a township settlement near Cape Town, and which integrated screening and short psycho-education by HIV counsellors for pregnant women who reported alcohol or substance use, found no improvement in alcohol use after three months (Sorsdahl *et al.*, 2015). More research is therefore needed to assess whether such interventions would be beneficial in reducing alcohol consumption among women at risk for depression.

Given the impact of depressive symptoms during the postpartum period, even if not chronically severe, as reported in Chapter 4, it is essential that children's growth be monitored on a regular basis and that any intervention for perinatal depression also include feeding and parenting elements to prevent impaired child growth and, consequently, prevent poor health outcomes later in childhood. There is some evidence that psychosocial interventions for perinatal depression alone are beneficial to children's development outcomes, which could be explained by the behavioural pathways between perinatal depression and child outcomes outlined earlier in this Chapter (Sohr-Preston and Scaramella, 2006). However, interventions for perinatal depression which also include parenting elements or education on feeding are most likely to be effective in both preventing impaired child development

and in reducing depressive symptoms (Parsons *et al.*, 2012). There is evidence from a recent study conducted in Uganda, for example, which assessed the effectiveness of a 12-session intervention focusing on both parentings skills and practices, as well as the psychological wellbeing of mothers of children between the ages of 12 and 36 months (Singla *et al.*, 2015). The study indicates that mothers who received the intervention had fewer depressive symptoms and their children had greater cognitive and language development scores compared to children of mothers who did not receive the intervention.

6.4.4. Perinatal mental health in South Africa: current status and way forward

The need to integrate the identification, treatment and management of mental disorders during pregnancy and postnatally, including alcohol and substance use, is recognised in the current South African National Mental Health Policy and Strategic Plan (Department of Health, 2013). However, it remains unclear how this is to be implemented nationally, and a system to identify women at risk for depression or suicide during pregnancy or postnatally in primary health care (PHC) facilities is still lacking.

Currently in South Africa, aside from the Eastern Cape, between 71% and 98% of pregnant women attend at least one antenatal session nationwide (Day *et al.*, 2018). The high attendance rates for antenatal care means that identifying women at risk for depression at their first antenatal visit may be a feasible strategy as a first point of contact. However, only 73% attend four antenatal visits or more (Department of Health, 2012), the minimum number of visits endorsed in the guidelines for maternal care in South Africa (Department of Health, 2015). Also, recommendations in relation to postnatal care indicate that mothers should attend the clinic within six days post-delivery and this is adhered to by on average 71% of mothers nationwide (Day *et al.*, 2018). Given the need to monitor women's depression and suicidal risk throughout the perinatal period, a community-based follow-up and monitoring care would be advisable.

Globally, the role of community-based services in providing mental health care has been expanding (Ventevogel, 2014). This has been in response to the difficulty of already overburdened primary health care staff to take on the delivery of mental health care as part of the task-sharing strategy advocated to reduce the mental health treatment gap in LMICs. Some have warned against the use of CHWs, who are often already stretched in the provision of HIV, immunisation, health education and family planning (Clarke *et al.*, 2013), the PHC Re-engineering plan tried to overcome this problem by allocating six CHWs and one nurse in each ward-based PHC outreach team. They now have clear

responsibilities towards i) providing antenatal and postnatal community-based support and intervention to reduce maternal mortality; ii) providing psychosocial support, iii) screening for early detection and intervention, and iv) providing follow-up and support (Naledi *et al.*, 2011). Outreach teams are also to be involved in providing basic information and education, as well as basic home-based health care for children under the age of five and referrals to social services and health facilities where appropriate (Naidoo, 2015).

Given the recommendations provided above for the identification, referral and monitoring needed to address the burden of perinatal depression among low-resource women in South Africa, and given the outreach CHWs' position in the community and responsibilities as outlined in the PHC re-engineering plan, it seems CHWs may have a key role in the provision of mental health care among perinatal women. More specifically, CHWs could be involved in following-up perinatal women at community level to identify and monitor those at risk for depression or suicide, and in triaging women who may only require social or peer support at community level from those who may benefit from more intensive psychological treatment or medication. This way, the extensive training and supervision required for the provision of psychosocial or psychological interventions by non-mental health professionals would be limited to PHC providers. Further implementation research is required to assess the feasibility of such monitoring and referral strategies, and to determine which cadre might be able to provide psychological interventions at PHC level in an effective and sustainable.

In sum, the present findings have clear implications on when and how perinatal women at risk for severe or chronic depressive symptoms and those at risk for suicide should be identified, referred and monitored. Findings also highlight the need to include education on feeding practices and maternal behaviours in interventions targeting perinatal women at risk for depression, including alcohol use during pregnancy and breastfeeding.

Chapter 7. Conclusion

This thesis sought to identify the trajectories of perinatal depressive symptoms among low-income women in South Africa, as well as to investigate their association with psychosocial and economic risk factors, child outcomes and suicidal risk over time. Despite methodological limitations to the study design and use of screening tools to assess depressive symptom severity, the findings make compelling evidence that perinatal women cannot be considered a homogenous group and that heterogeneous trajectories of depressive symptoms are reported globally. Importantly, a minority of women show a trajectory of severe and chronic depressive symptoms, indicating that women belonging to this high-risk group show symptoms that will not abate naturally and may need to be referred to more intensive psychological treatment or medication. The high-risk psychosocial profiles of women with severe and chronic depressive symptoms mean this group can be identified early on in pregnancy to prevent worsening of symptoms and prevent further health complications for the mothers and their children. The findings also highlight the importance of taking the social determinants of mental health into account in the identification of perinatal depression in low-income settings. The impact of depressive symptoms during the postnatal period, even if not chronic, on children's physical and socio-emotional development points to the need for an identification, referral and treatment system that addresses all levels of symptom severity, however.

Despite the criteria of current classifications, women remain at risk for depression later in the postpartum period, so it is essential that women's depressive symptoms be monitored throughout the perinatal period, and not just at the first antenatal visit or within the first month after giving birth. Further research is needed to identify ways of differentiating women with chronically mild symptoms from those who see their symptoms worsen later in the postpartum period as results were inconclusive in the present thesis.

Women's depressive symptoms and suicidal risk are best considered overlapping but independent phenomena, and must be assessed and monitored accordingly. This is particularly important among older women or women who report more severe and chronic trajectories of depressive symptoms. There is a need for future research to take into consideration the heterogeneity in suicidal risk, as well as in depressive symptom profiles when assessing trajectories of perinatal depressive symptoms.

The findings have direct implications for the provision of perinatal mental health care in South Africa, especially relating to the identification and referral of women at risk for depression or suicide. Despite the implementation of the re-engineering of primary health care and the fact that a policy and strategic plan are in place for the provision of mental health care in South Africa, mental health services for perinatal women remains limited. The present preliminary findings provide some indication that not all women at risk for depression may need to same level of care, and that referral systems to services at the community or primary health care level should be developed with women's risk of severe or chronic depressive symptoms in mind; this is bound to help make use of the available current resources more efficiently.

The research presented in this thesis is the first to investigate latent trajectories of perinatal depressive symptoms in relation to risk factors and child development in Sub-Saharan Africa. More research is clearly needed to assess the validity of the findings presented here. Clear recommendations were made on how to optimise the use of GCMM in future research after having systematically reviewed the literature on the use of GCMM to identify latent trajectories of depressive symptoms among perinatal women and after having made use of such methods in two different samples in a low-income setting. Based on these recommendations, researchers should be able to generate stronger evidence on the different course and consequences of different trajectories of perinatal depression in low-income settings. Used together with other growth curve methods, this could ultimately contribute towards improving our understanding of perinatal depression in low-income countries, developing more efficient identification, referral and treatment strategies, and reducing the burden of perinatal depression on mothers and their children.

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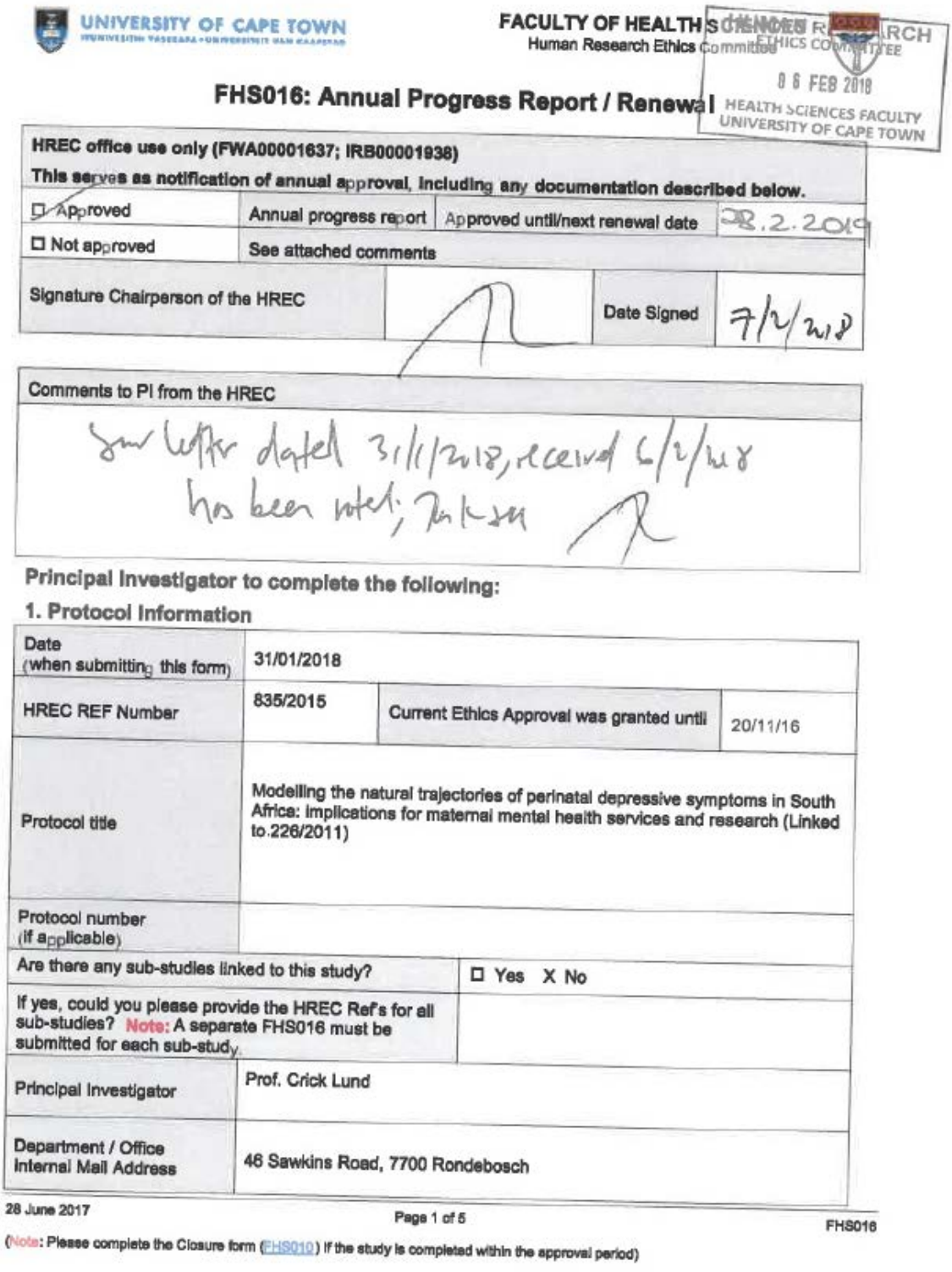
Appendices

Appendix A. Ethics approval for the present thesis



UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HEALTH SCIENCES RESEARCH ETHICS COMMITTEE
06 FEB 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	28.2.2019
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	7/2/2018

Comments to PI from the HREC
Your letter dated 31/1/2018, received 6/2/2018 has been noted; Thank you

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	31/01/2018		
HREC REF Number	835/2015	Current Ethics Approval was granted until	20/11/16
Protocol title	Modelling the natural trajectories of perinatal depressive symptoms in South Africa: implications for maternal mental health services and research (Linked to 226/2011)		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes X No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof. Crick Lund		
Department / Office Internal Mail Address	46 Sawkins Road, 7700 Rondebosch		

28 June 2017 Page 1 of 5 FHS016

(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)

Appendix B. Motivation letter for inclusion of publications in the present thesis

Alan J Flisher Centre
for Public Mental Health

Monday, 5th November 2018

Prof Mike Lambert
Chair of the Masters and Doctoral Committee
Faculty of Health Sciences
University of Cape Town

Dear Prof Lambert,

Letter of motivation for PhD thesis by publication

I am currently completing my PhD under the supervision of Prof Crick Lund and A/Prof Marguerite Schneider. I am planning on submitting my PhD thesis in February 2019, which is entitled *"The natural trajectories of depressive symptoms in South Africa"*. My candidature was approved by UCT's Doctoral Degrees Board (DDB) on 22 September 2016. Since then, my supervisors and I have indicated in the Memorandum of Understanding that I wish to include published articles in my PhD thesis, or articles which are currently under review. Now that I am nearing completion of my PhD, I am writing this letter to ask the DDB permission to include publications in my thesis.

As indicated in the UCT guidelines, I will ensure that the publications form part of a "thematically coherent" thesis and ensure that each publication answers a specific objective of my PhD. The overall aim of my PhD is to use latent modelling techniques to identify the different natural trajectories of women suffering from depressive symptoms during the perinatal period, in order to make recommendations for detection and treatment strategies, given the limited mental health resources available at primary care level in South Africa, and to inform future research in the field. To that effect, I would like to include four publications in my thesis as chapters, each of which answer a specific objective. My thesis will also include an introduction, which will consist of a thorough review of the literature, as well as a discussion section which will reflect on the findings of the thesis as a whole.

So far, one article has been published, two are under review, and one is drafted but not yet submitted. I am the lead author on all four articles. However, I conducted secondary analyses on data already collected from two projects, the Africa Focus on Intervention Research for Mental Health and the Philani Intervention Programme study, therefore other researchers were also involved. All co-authors are aware that these publications will be included in my PhD thesis, and none of them are currently PhD students. Find attached a letter from my supervisor, Prof Crick Lund, confirming that the co-authors have given their permission to include these papers as part of my PhD.

A brief description of my PhD objectives and how each paper addresses these is provided below.

Emily Baron
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Objective 1: To systematically review the literature on the different trajectories of perinatal depressive symptoms and associated risk and symptom profiles.

- Status: Published
- Reference: Baron EC, Bass J, Murray SM, Schneider M, Lund C. A systematic review of growth curve mixture modelling literature investigating trajectories of perinatal depressive symptoms and associated risk factors. Journal of Affective Disorders. 2017; 223:194-208.
- Contributions: I conceptualised the article, conducted the systematic search and drafted this article, under the guidance of my supervisors. Judith Bass and Sarah Murray contributed as independent researchers to screen articles to be included in the systematic review.

Objective 2: To identify latent trajectories of perinatal depressive symptoms and associated factors during pregnancy and up to one year postpartum, as a secondary analysis of the AFFIRM trial.

- Status: Under review
- Reference: Baron EC, Schneider M, Lund C. Perinatal depressive symptoms among low-income South African women: trajectories and predictors. BMC Psychiatry. 2018; Under review.
- Contributions: I conceptualised the article, conducted the analyses and drafted the article, under the guidance of my supervisors

Objective 3: To identify latent trajectories of perinatal depressive symptoms and child outcomes, as a secondary analysis of the Philani Intervention Programme study

- Status: Under review, reviewers' comments received
- Reference: Baron EC, Cois A, Tomlinson M, Rotheram-Borus MJ, Lund C. Course of perinatal depressive symptoms among South African women: associations with child outcomes at 18 and 36 months old. Social Psychiatry and Psychiatric Epidemiology. 2018; Under review.
- Contributions: I conceptualised the article, conducted the analyses and drafted the article, under the guidance of my supervisors. Annibale Cois provided statistical support with the programme Mplus, whereas Mark Tomlinson and Mary Jane Rotheram-Borus were the principle investigators on the Philani Intervention Programme study, and therefore provided guidance on the study as a whole and ensured the correct interpretation of the data.

Emily Baron
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Alan J Flisher Centre
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Objective 4: To investigate the association between depressive symptoms and suicidal behaviours over time among pregnant and postnatal women in a low-resource setting, as a secondary analysis of the AFFIRM trial.

- Status: Drafted, not yet submitted
- Title: Baron EC, Cois A, Schneider M, Lund C. Association between perinatal depressive symptoms and suicidal risk in low-income South African women: a longitudinal study
- Contributions: I conceptualised the article, conducted the analyses and drafted the article, under the guidance of my supervisors. Annibale Cois provided support with the analysis plan.

I would be grateful if you could provide permission for me to include the above publications in my PhD thesis.

Many thanks and kind regards,

Emily Baron

Emily Baron
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Appendix C. Mental health screen to be included in the Maternity Case Records (Chapter 6)

MENTAL HEALTH SCREEN

ONLY to be conducted if resources are available for referral, e.g. mental health nurse, social worker, NGO, medical officer, counsellor, psychiatrists or other services.

Suggested words to use before screening.

"We would like to know about all the women who come here: how they are doing physically and emotionally. This helps us to understand the best sort of care we can offer. Please may I ask you three questions about how you are emotionally? Please answer 'yes' or 'no' to each question."

In the last 2 weeks, have you on some or most days felt unable to stop worrying or thinking too much?	☐ Yes [1]	☐ No [0]
In the last 2 weeks, have you on some or most days felt down, depressed or hopeless?	☐ Yes [1]	☐ No [0]
In the last 2 weeks, have you on some or most days had thoughts **and** plans to harm yourself or commit suicide?*	☐ Yes [1] **Refer**	☐ No [0]
TOTAL SCORE	☐ 1 ☐ 2 >>>>>>>>>>> refer ☐ 3 >>>>>>>>>>> refer	
Offered Counselling	☐ Yes	☐ No
Accepted counselling	☐ Yes	☐ No

**the self-harm question will require urgent referral if there are both thoughts AND plans. If there is a history of previous attempt, referral is required even if there are thoughts alone.*

Appendix D. Main clinical instruments included in the assessment of the AFFIRM randomised controlled trial (Chapters 3 and 5)

Hamilton Depression Rating Scale		
During the past month, have you been less able than usual to work or do your usual activities? Do your activities make you feel tired, or have you lost interest in your activities?	0 1 2 3 4	No decrease in productivity or time spent at work and/or doing usual activities Activities make you feel tired Lost interest in work or activities Decrease in productivity or work or activities Spending less time at work or doing activities
Have you gained or lost any weight during the past month?	0 1 2	No Possibly Yes, definite change in weight (not on diet)
During the past month, have you experienced a loss of appetite?	0 1 2	No loss of appetite Some loss of appetite but still eating At least some loss of interest in food and requires encouragement to eat
During the past month, have you had an interest in sex?	0 1 2	Yes, normal interest in sex (or is not sexually active) Somewhat less interest A lot less interest than usual or no interest at all
During the past month, have you had troubles or difficulties falling asleep?	0 1 2	No Sometimes Yes, almost every night has difficulty
During the past month, have you been waking up during the night?	0 1 2	No Sometimes Yes, almost every night has difficulty and gets out of bed, other than for urinating/peeing
During the past month, have you either been waking up earlier in the morning than you wanted to or sleeping too much?	0 1 2	No Sometimes Yes, wakes early and cannot go back to sleep, or sleeps too much most of the time
During the past month, have you experienced fatigue or had less energy than usual? Or have you had headaches, backaches, or aches in specific parts of your body?	0 1 2	No loss of energy, fatigue, or body aches Some loss of energy and body aches Yes, marked loss of energy, and/or has a clear symptom of pain, e.g., headaches, or local muscle aches
During the past month, have you been feeling guilty or bad about something you have done? Do you feel you have let people down or that you are evil? Do you think your illness is punishment for something?	0 1 2 3 4	No guilty feelings Feels she has let people down OR feels evil or bad Feels she has let people down AND feels evil or bad Thinks that her illness is a punishment Hears voices or feels that her badness will hurt others or will lead to her own death
During the past month, have you been feeling nervous, anxious, worried or frightened?	0 1 2 3 4	Never Sometimes Quite often Most of the time Yes, severe symptoms all the time which are incapacitating or disabling
Tell me if you experience any of these and how severe they are: Stomach or digestive problems or pains	0 1	No Yes
Heart palpitations	0 1	No Yes
Breathing very fast or trouble breathing	0 1	No Yes
Urinating often	0 1	No Yes
Muscle aches, body aches	0	No

	1	Yes
Unusual sensations like trembling or ringing in your ears	0 1	No Yes
Flushing, feeling faint, or sweating	0 1	No Yes
None of these	0 1	No Yes
How would you rate the most severe of these physical symptoms?	0 1 2 3 4	Absent A little bit Some A lot Severe and incapacitating problem
During the past month, have you been worrying more than usual about your health and how your body is working? (Apart from normal fears about your pregnancy)	0 1 2 3 4	Not worried at all Some unnecessary worry about her health A lot of unnecessary worry about her health Strong beliefs she has a physical problem and doctors won't believe her Delusional, i.e. has false beliefs, e.g. Thinks her body is rotting
During the past month, have you had thoughts that life is not worth living, or that you would rather be dead? Have you had thoughts of hurting or killing yourself?	0 1 2 3 4	No Sometimes Often Most of the time Suicide attempt
Do you think that you have a psychological problem, such as depression?	0 1 2	Acknowledges being depressed or having a psychological problem (OR is not currently depressed) Acknowledges illness but blames it on something else Denies any illness but is currently depressed in interviewer's opinion
During the past month, have you been feeling sad, depressed, helpless, hopeless, or worthless? If yes, how often do you feel this way?	0 1 2 3 4	Not at all Occasionally Quite often Very often Yes, almost all of the time
Observe and rate slowness of thought, speech, concentration, and physical movement	0 1 2 3 4	Normal speech and thought Slight retardation (a bit of slowness in thinking or speaking) Obvious retardation (a lot of slowness in thinking or speaking) Interview difficult (a lot of very long pauses) Interview impossible
Observe and rate restlessness, fidgetiness and physical activity	0 1 2 3 4	None Fidgetiness Playing with hands, hair, obvious restlessness (restless, unfocused, playing with hands or clothes) Moving about, can't sit still Hand wringing, nail biting, hair pulling, biting of lips, patient is moving about a lot

Edinburgh Postnatal Depression Scale		
I have been able to laugh and see the funny side of things	0 1 2 3	As much as I always could Not quite so much now Definitely not so much now Not at all
I have looked forward with enjoyment to things	0 1 2 3	As much as I ever did Rather less than I used to Definitely less than I used to Hardly at all
I have blamed myself unnecessarily when things went wrong	3 2 1 0	Most of the time Some of the time Not very often No never
I have been anxious or worried for no good reason	0 1 2 3	Not at all Hardly ever Sometimes Very often
I have felt scared or panicky for no very good reason	3 2 1 0	Quite a lot Sometimes Not much Not at all
Things have been getting on top of me	3 2 1 0	Most of the time not coping at all Sometimes not coping as well as usual Most of the time coped quite well Coping as well as ever
I have been so unhappy that I have had difficulty sleeping	3 2 1 0	Most of the time Sometimes Not very often Not at all
I have felt sad or miserable	3 2 1 0	Most of the time Sometimes Not very often Not at all
I have been so unhappy that I have been crying	3 2 1 0	Most of the time Quite often Only occasionally Never
The thought of harming myself has occurred to me	3 2 1 0	Quite often Sometimes Hardly ever Never

MINI Depression module		
	Yes	No
Were you ever depressed or down, most of the day, nearly every day, for two weeks?	1	0
For the past two weeks, were you depressed or down, most of the day, nearly every day?	1	0
Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	1	0
In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	1	0
How many episodes of depression did you have in your lifetime? (Between each episode there must be at least 2 months without any significant depression)		
Was your appetite decreased or increased nearly every day over the past 2-week period? Did you weight decrease without trying intentionally?	1	0
During episodes of depression in the past, was your appetite decreased or increased? Did your weight decrease without trying intentionally?	1	0
Did you have trouble sleeping nearly every night over the past 2-week period (Difficulty falling asleep, waking in the middle of the night, early morning wakening or sleeping excessively)?	1	0
During episodes of depression in the past, did you have trouble sleeping nearly every night (Difficulty falling asleep, waking in the middle of the night, early morning wakening or sleeping excessively)?	1	0
Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day over the past 2-week period?	1	0
During episodes of depression in the past, did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	1	0
Did you feel tired or without energy almost every day over the past 2-week period?	1	0
During past episodes of depression in the past, did you feel tired or without energy almost every day?	1	0
Did you feel worthless or guilty almost every day over the past 2-week period?	1	0
During episodes of depression in the past, did you feel worthless or guilty almost every day?	1	0
Did you have difficulty concentrating or making decisions almost every day over the past 2-week period?	1	0
During episodes of depression in the past, did you have difficulty concentrating or making decisions almost every day?	1	0
Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead over the past 2-week period? Did you attempt suicide or plan a suicide?	1	0
During episodes of depression in the past, did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? Did you attempt suicide or plan a suicide?	1	0
Did these symptoms cause significant problems at home, at work, socially, at school or in some other important way over the past 2-week period?	1	0
During episodes of depression in the past, did these symptoms cause significant problems at home, at work, socially, at school or in some other important way?	1	0
In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest?	1	0

MINI Suicidality module			
	No		Yes
In the last month, did you suffer from any accident? This includes taking too much of your medication accidentally.	0		1
In the last month, did you plan or intend to hurt yourself in any accident either actively or passively (e.g. by not avoiding a risk)?	0		1
In the last month, did you intend to die as a result of any accident?	0		1
In the last month, did you feel hopeless?	0		1
In the last month, did you think that you would be better off dead or wish you were dead?	0		1
In the last month, did you think about hurting or injuring yourself or have mental images of harming yourself, with at least some intent or awareness that you might die as a result?	0		1
About how many times did you think about this in the last month?			
In the last month, did you think about suicide (killing yourself)?	0		1
About how many times did you think about killing yourself in the last month?			
	Occasion-ally	Often	Very often
How often did you think about killing yourself?	1	2	3
	Mild	Mode-rate	Severe
What was the intensity of these thoughts?	1	2	3
Did you feel unable to control these impulses?	0		8
In the last month, did you have a suicide method or plan in mind (e.g. how, when or where)?	0		8
In the last month, did you intend to follow through on a suicide plan?	0		6
In the last month, did you intend to die as a result of a suicidal act?	0		8
In the last month, did you take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	0		9
How many times?			
In the last month, did you injure yourself on purpose without intending to kill yourself?	0		4
In the last month, did you attempt suicide (to kill yourself)? [Note: A suicide attempt means you did something where you could possibly be injured with at least a slight intent to die.]	0		9
How many times?	1		0
Did you Hope to be rescued/survive? Or did you expect/intend to die?	1 2		
In your lifetime, have you ever made a suicide attempt (try to kill yourself)?	0		4

WHODAS Disability Assessment Schedule					
	None	Mild	Moderate	Severe	Cannot do
In the last 30 days, how much difficulty did you have with standing for long periods such as 30 minutes?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with taking care of your household responsibilities?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with learning a new task, for example, learning how to get to a new place?	1	2	3	4	5
In the last 30 days, how much problem did you have joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	1	2	3	4	5
In the last 30 days, how much have you been emotionally affected by your health problems?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with concentrating on doing something for ten minutes?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with walking a long distance such as a kilometer [or equivalent]?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with washing your whole body?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with getting dressed?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with dealing with people you do not know?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with maintaining a friendship?	1	2	3	4	5
In the last 30 days, how much difficulty did you have with your day to day work?	1	2	3	4	5
Overall, in the past 30 days, how many days were these difficulties present?					
In the past 30 days, for how many days were you totally unable to carry out your usual activities or work because of any health condition?					
In the past 30 days, not counting the days that you were totally unable, for how many days did you cut back or reduce your usual activities or work because of any health condition?					

Cape Town Functional Assessment Instrument						
Thinking about the last two weeks, how much difficulty do you have doing the following tasks and activities:						
	No difficulty	A little or some difficulty	A lot of difficulty	Often can't do task	Can never do task	Not applicable
Cleaning the house	0	1	2	3	4	5
Preparing and cooking food for the family	0	1	2	3	4	5
Doing laundry	0	1	2	3	4	5
Bathing yourself	0	1	2	3	4	5
Taking part in community meetings	0	1	2	3	4	5
Taking care of physical needs of babies and children (bathing, feeding, preparing for crèche or school, taking to crèche and school, keeping them safe, etc.)	0	1	2	3	4	5
Playing with your children and loving them	0	1	2	3	4	5
Spending time and doing activities with family and friends	0	1	2	3	4	5
Exercising	0	1	2	3	4	5
Doing volunteer work	0	1	2	3	4	5

Alcohol Use Disorder Identification Test					
	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How often do you have a drink containing alcohol?	0	1	2	3	4
	1-2	3-4	5-6	7-9	10 or more
How many drinks containing alcohol do you have on a typical day when you are drinking?	0	1	2	3	4
	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often do you have six or more drinks on one occasion?	0	1	2	3	4
How often during the last year have you found that you were not able to stop drinking once you had started?	0	1	2	3	4
How often during the last year have you failed to do what was normally expected of you because of drinking?	0	1	2	3	4
How often during the last year have you needed a drink in the morning to get yourself going after a heavy drinking session?	0	1	2	3	4
How often during the last year have you had a feeling of guilt or remorse after drinking?	0	1	2	3	4
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	0	1	2	3	4
	No	Yes, but not in the last year		Yes, during the last year	
Have you or someone else been injured as a result of your drinking?	0	1		2	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?	0	1		2	

Household Food Insecurity Assessment Scale				
	Never	Rarely	Sometimes	Often
Did you worry that your household would have enough food? [in past 30 days]	0	1	2	3
Were you or any household member not able to eat the kinds of foods you preferred because of a lack of resources?	0	1	2	3
Did you or any household member eat just a few kinds of food day after day due to a lack of resources?	0	1	2	3
Did you or any household member eat food that you preferred not to eat because of a lack of resources to obtain other types of food?	0	1	2	3
Did you or any household member eat a smaller meal than you felt you needed because there was not enough food?	0	1	2	3
Did you or any household member eat fewer meals because there was not enough food?	0	1	2	3
Was there ever no food at all in your household because there was not enough resources to get more?	0	1	2	3
Did you or any household member go to sleep at night hungry because there was not enough food?	0	1	2	3
Did you or any household member go a whole day without eating anything because there was not enough food?	0	1	2	3

Multidimensional Scale of Perceived Social Support							
	Very strongly disagree	Strongly disagree	Mildly disagree	Neutral	Mildly agree	Strongly agree	Very strongly agree
There is a special person who is around when I am in need	1	2	3	4	5	6	7
There is a special person with whom I can share my joys and sorrows	1	2	3	4	5	6	7
My family really tries to help me	1	2	3	4	5	6	7
I get the emotional help and support I need from my family	1	2	3	4	5	6	7
I have a special person who is a real source of comfort to me	1	2	3	4	5	6	7
My friends really try to help me	1	2	3	4	5	6	7
I can count on my friends when things go wrong	1	2	3	4	5	6	7
I can talk about my problems with my family	1	2	3	4	5	6	7
I have friends with whom I can share my joys and sorrows	1	2	3	4	5	6	7
There is a special person in my life who cares about my feelings	1	2	3	4	5	6	7
My family is willing to help me make decisions	1	2	3	4	5	6	7
I can talk about my problems with my friends	1	2	3	4	5	6	7

Interpersonal violence		
	Yes	No
Have you been a victim of physical violence in the last 3 months? (E.g. beating, pushing, kicking, biting, slapping etc.)	0	1
Who abused you physically? (Select all that apply)		
Partner	0	1
Relative	0	1
Friend	0	1
Stranger	0	1
Acquaintance	0	1
Have you been a victim of sexual violence in the last 3 months?	0	1
Who abused you sexually? (Select all that apply)		
Partner	0	1
Relative	0	1
Friend	0	1
Stranger	0	1
Acquaintance	0	1

HIV status				
	No (0)	Yes (1)	Refused (98)	
Do you know your HIV status?	0	1	98	
What is your HIV status?	0	1	98	
When did you find out your HIV status?	Today (1)	In the last month (2)	In the last 6 months (3)	Longer ago (4)
Do you know the date of your most recent HIV test?	0	1	98	
What was the date of your most recent HIV test?				

Appendix E. Ethics approval for the AFFIRM randomised controlled trial

HUMAN RESEARCH ETHICS COMMITTEE
18 MAY 2015
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	28.4.2016
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	rp TJBurgess	Date Signed	20/05/2015

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	12 May 2015		
HREC REF Number	226/2011	Current Ethics Approval was granted until	17 May 2015
Protocol title	COLLABORATIVE HUBS FOR INTERNATIONAL RESEARCH ON MENTAL HEALTH (U19): AFRICA FOCUS ON INTERVENTION RESEARCH FOR MENTAL HEALTH (AFFIRM) **AFFIRM-SA trial (South Africa) and TaSCS trial (Ethiopia)**		
Protocol number (if applicable)	12161949		
Are there any sub-studies linked to this study?	☐ Yes X No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof Crick Lund		
Department / Office Internal Mail Address	Psychiatry and Mental Health		

1.1 Does this protocol receive US Federal funding?	X Yes	☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	X No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	X No

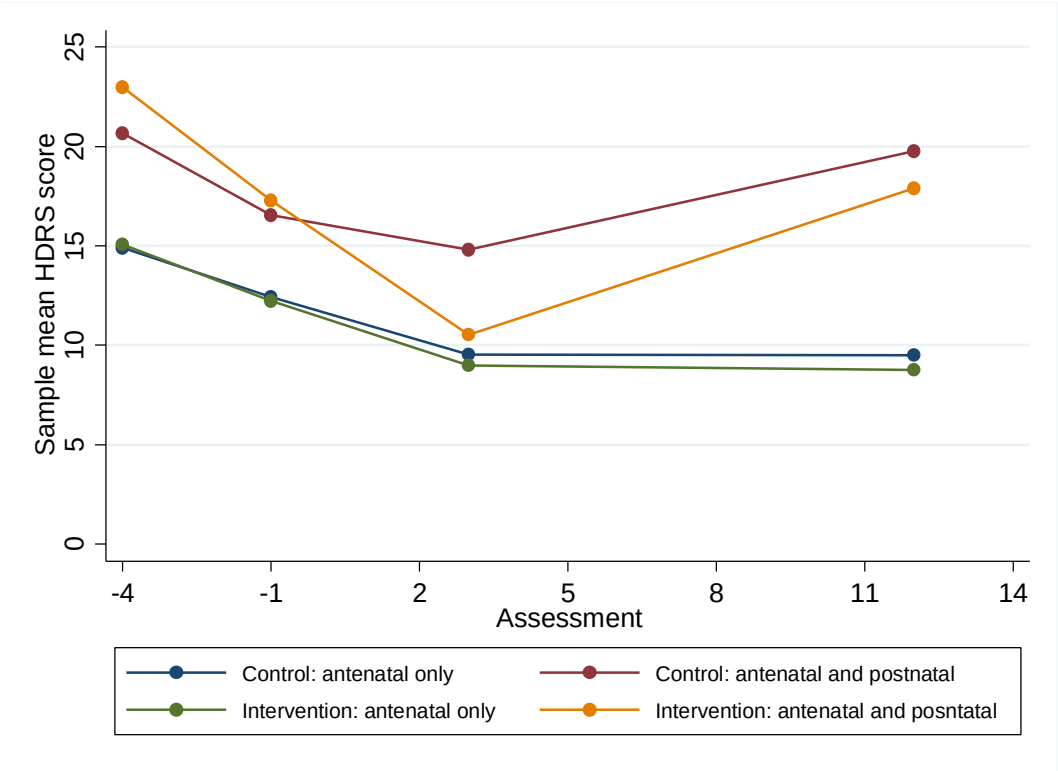
(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix F. Latent class growth analysis and growth mixture modelling, per arm (Chapter 3)

				Size (%) of smallest class	
Classes	BIC	AIC	Entropy	Control	Intervention
Quadratic LCGA [a]					
2	8380.171	8305.108	0.876	12.0 (23.0% within arm)	12.8 (26.6% within arm)
3	8385.351	8278.683	0.862	2.9 (5.5% within arm)	0.5 (1.1% within arm)
4	8405.255	8266.983	0.816	2.6 (5.0% within arm)	0.5 (1.1% within arm)
Quadratic GMM [b]					
2	**8355.436**	**8260.621**	**0.911**	**5.5 (10.5% within arm)**	**3.9 (8.2% within arm)**
3	8377.072	8250.651	0.863	1.8 (3.5% within arm)	4.2 (8.7% within arm)
4	8402.664	8244.638	0.860	0.5 (1% within arm)	0.3 (0.5 % within arm)

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; [a] Latent curve growth analysis; [b] growth mixture modelling.

Appendix G. Means HDRS curves of the 2-class growth mixture model, per arm (Chapter 3)



Appendix H. Main clinical instruments included in the assessment of the Philani cluster randomised controlled trial (Chapter 4)

Edinburgh Postnatal Depression Scale		
I have been able to laugh and see the funny side of things	0 1 2 3	As much as I always could Not quite so much now Definitely not so much now Not at all
I have looked forward with enjoyment to things	0 1 2 3	As much as I ever did Rather less than I used to Definitely less than I used to Hardly at all
I have blamed myself unnecessarily when things went wrong	3 2 1 0	Most of the time Some of the time Not very often No never
I have been anxious or worried for no good reason	0 1 2 3	Not at all Hardly ever Sometimes Very often
I have felt scared or panicky for no very good reason	3 2 1 0	Quite a lot Sometimes Not much Not at all
Things have been getting on top of me	3 2 1 0	Most of the time not coping at all Sometimes not coping as well as usual Most of the time coped quite well Coping as well as ever
I have been so unhappy that I have had difficulty sleeping	3 2 1 0	Most of the time Sometimes Not very often Not at all
I have felt sad or miserable	3 2 1 0	Most of the time Sometimes Not very often Not at all
I have been so unhappy that I have been crying	3 2 1 0	Most of the time Quite often Only occasionally Never
The thought of harming myself has occurred to me	3 2 1 0	Quite often Sometimes Hardly ever Never

Alcohol Use Disorder Identification Test - C		
Now that you know you are pregnant,		
About how often do you drink ANY alcoholic beverage?	1 2 3 4 5 6 7 8 9 91	Never Less than once a month Once a month 2 to 3 times a month Once a week 2 times a week 3 to 4 times a week Nearly every day Every day Decline to answer
Counting all types of alcohol combined, how many drinks to you USUALLY have on days when you drink alcohol	1 2 3 4 5 91	1 or 2 3 or 4 5 or 6 7 to 9 10 or more Decline to answer
About how often do you drink THREE or MORE drinks in a single day?	1 2 3 4 5 6 7 8 9 91	Never Less than once a month Once a month 2 to 3 times a month Once a week 2 times a week 3 to 4 times a week Nearly every day Every day Decline to answer

Social support	
How many close friends and relatives do you have? By this, I mean people you feel at ease with and can talk with about what is on your mind	
In this past month, approximately how many times have you had contact with friends or relatives (including visits, phone calls, sms, and social gatherings)?	

HIV status		
Do you know your HIV status?	0 1 91	No Yes Decline to answer
When were you last tested for HIV?		
What was the result of your test?	0 1 91	No Yes Decline to answer

Intimate partner violence				
	Never	Once	Few	Many
In the past 12 months, did your current partner or any other boyfriend slap you or throw something at you which could hurt you? Did this happen many times, a few times, once or did not happen?	1	2	3	4
IN the past 12 months, did your current partner or any other boyfriend push or shove you? Did this happen many times, a few times, once or did it not happen?	1	2	3	4
In the past 12 months, did your current partner or any other boyfriend hit you with a fist or something else which could hurt you? Did this happen many times, a few times, once or did it not happen?	1	2	3	4
In the past 12 months, did your current partner or any other boyfriend threaten to use or actually use a gun, knife or other weapon against you? Did this happen many times, a few times, once or did it not happen?	1	2	3	4

Appendix I. Ethics approval for the Philani cluster randomised controlled trial

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Progress Report Approval Letter

21/06/2018

Project Reference #: 3112

Ethics Reference #: N17/02/014

Title: Longitudinal Study to Measure the Impact of a Maternal and Child Health/Nutrition Intervention on Maternal and Child Health and child cognitive development at aged 8 years.

Dear Prof Mark Tomlinson ,

Your request for extension/annual renewal of ethics approval dated 06 May 2017 refers.

The Health Research Ethics Committee reviewed and approved the annual progress report you submitted through an expedited review process.

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

Approval date: 21 June 2018

Expiry date: 20 June 2019

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

Where to submit any documentation

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

Please remember to use your **Project ID** [3112] and Ethics Reference Number [N17/02/014] on any documents or correspondence with the HREC concerning your research protocol.

National Health Research Ethics Council (NHREC) Registration Numbers: REC-130408-012 for HREC1 and REC-230208-010 for HREC2

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005240 for HREC1

Institutional Review Board (IRB) Number: IRB0005239 for HREC2

The Health Research Ethics Committee complies with the SA National Health Act No. 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki and the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles, Structures and Processes 2015 (Department of Health).

Yours sincerely,

Miss Elvira Rohland

Health Research Ethics Committee 1

Appendix J. Mean HDRS curves of the alternative 3-class growth mixture model among the high-risk perinatal population in Khayelitsha (Chapter 6)