Perinatal depression and adverse infant outcomes among Kenyan mother-infant pairs

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Abstract

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Pregnancy and postpartum are periods of high vulnerability to mental disorder. More than 1 in 10 women experience a mental disorder during pregnancy and 13% after delivery, most commonly depression. Pregnancy and postpartum are critical time periods for the health and survival of mothers and their infants, yet maternal depression, remains underprioritized. Women in low- and middle-income countries (LMICs) are disproportionately affected by maternal depression. Despite the high burden of maternal mental health difficulties in LMICs, gaps remain in the evidence-base, particularly in LMICs of sub-Saharan Africa where maternal and neonatal morbidity remain high such that addressing perinatal depression could have high impact.

Screening tools for depression have not been formally evaluated for their performance in busy sub-Saharan Africa maternal child health clinics. Further, manifestation and trajectory of maternal depression has not been adequately researched in sub-Saharan Africa. Links between maternal depression, adolescence, and poor neonatal health are well-established globally, but have not been extensively explored among Africa mother-infant pairs.

In the following dissertation aims, we address these gaps. In Chapter 2, we synthesize evidence depicting relative strength (low, medium, high) of perinatal depression screening scales for use among African pregnant and postpartum women within four quadrants: 1) diagnostic performance, 2) cultural adaptation, 3) feasibility and ease of implementation, 4) evidence-base from SSA settings. In Chapter 3, we compared the Edinburgh Postnatal Depression Scale (EPDS), Patient Health Questionnaire-9 (PHQ-9), Patient Health Questionnaire-2 (PHQ-2), and Center for Epidemiologic Studies Depression Scale (CESD-10) for diagnostic yield, symptomatologies, detection of epidemiologic associations with known cofactors of perinatal depression, and diagnostic performance to detect depression. In Chapter 4, to our knowledge,

our team performed the first perinatal depressive symptoms trajectory analysis in a LMIC setting that involved evaluation of time-varying correlates. In Chapter 5, we performed two evaluations among a cohort of Kenyan women living with HIV (WLWH). The first, Chapter 5a, we aimed to understand which WLWH are most at-risk for depression in pregnancy, as well as the magnitude of influence of associated correlates, thus we estimated the prevalence and cofactors of depression during pregnancy and the population attributable risk percent among this population. In Chapter 5b, we identified trajectories and predictors of postpartum depression among WLWH followed through 24 months postpartum to further inform efficient mental health resource allocation within PMTCT programs. In Chapter 6, we evaluated potential relationships between multiple psychosocial factors (depression, low social support, intimate partner violence) and multiple adverse perinatal outcomes (pregnancy loss, stillbirth, preterm birth, low birthweight, small-for-gestational age, and neonatal death) among a large cohort of Kenyan women.

Altogether, these results highlight the need for integrated mental health, maternal child health, and HIV prevention and treatment services to alleviate maternal mental distress and linked maternal-infant health outcomes to promote dyadic well-being.

TABLE OF CONTENTS

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DEDICATION

To all women and girls – may the freedom of good health pave the way to your dreams.

Chapter 1. Introduction

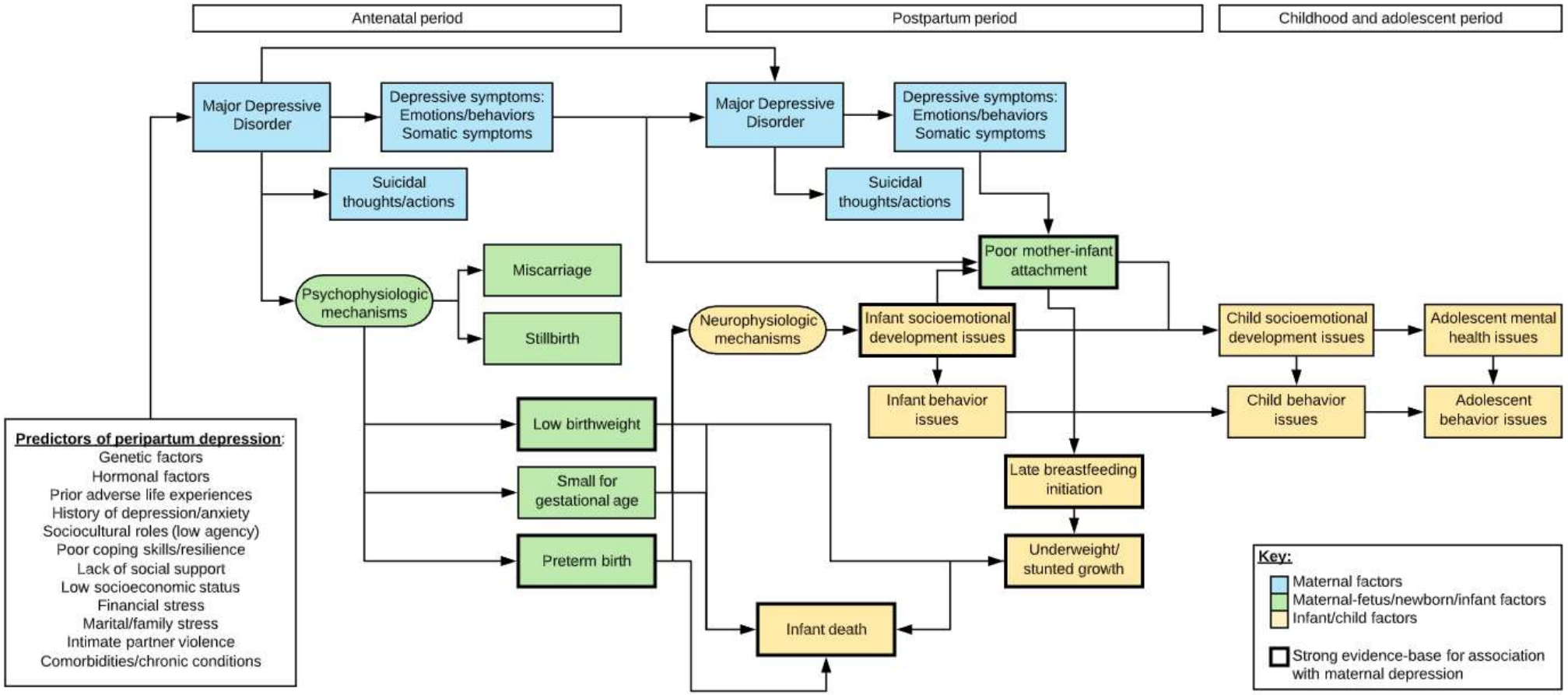
Background:
Perinatal depression and adverse infant outcomes among Kenyan mother-infant pairs

Mental disorder is the leading cause of disability burden worldwide**,** accounting for over 10% of global disability-adjusted life years[1], and the second leading cause of death (17% of deaths)[1]. As disease burden globally continues to shift from predominantly communicable to noncommunicable disease (NCD) under the epidemiologic transition[2], the NCD burden is shifting toward a higher proportion of neuropsychiatric disorders[3–5]. Globally, depressive disorders are among the top three causes of years lived with disability[6], account for 40% of all mental illness[5], and affect 350 million people comprising 4% of the population.[7] Women are disproportionally burdened by depression, with double the lifetime risk than their male counterparts[8,9]. Periods of biological change in women's lives are characterized by higher risk for depression[4,10].

Pregnancy and postpartum are periods of high vulnerability to mental disorder. More than 1 in 10 women experience a mental disorder during pregnancy and 13% after delivery[11–13], most commonly depression[12]. Hormonal shifts during these periods of biological change are widely implicated as important causes of mental disorder[13,14] (Figure 1.1). Pregnancy in adolescence leads to additive physiologic and psychosocial alterations between the parallel biological changes of teenage development and childbearing, putting pregnant adolescents at high risk for depression[15,16]. Pregnancy and postpartum are critical time periods for the health and survival of mothers and their infants[10,17,18], yet maternal depression, remains underprioritized[4].

Women in low- and middle-income countries are disproportionately affected by maternal depression. A systematic review and meta-analysis of maternal depression from 47 studies across 17 low- and middle-income countries (LMICs) revealed even higher prevalence of maternal depression than seen in high-income countries (HICs), identifying 15.6% (95% confidence interval (CI): 15.4 – 15.9) prevalence of antenatal depression and 19.8% (95% CI: 19.5 – 20.0) postnatally.[19] While the burden of maternal depression in LMICs is high, of further

Figure 1.1. Evidence-based and hypothesized relationships between maternal major depressive disorder, depressive symptoms, and perinatal, infant, and child health outcomes



References for figure components: Major depressive disorder, depressive symptoms (Woody, Gavin, Fisher); Predictors of peripartum depression (Payne, Stein, Lancaster, Kramer, Howard, Biaggi); psychophysiologic mechanisms (Payne); Low birthweight (Jarde, Grigoriadis); Small for gestational age (Jarde, Van Dijik), Preterm birth (Jarde, Grote, Grigoriadis); Neurophysiologic mechanisms (Stein); Infant death (Jacques); Infant socioemotional development issues (Madigan); Infant behavior issues (Stein, Gentile, Herba, Kingston); Poor mother-infant attachment (Barnes & Theule); Late breastfeeding initiation (Grigoriadis); Underweight/stunted growth (Surkan); Child socioemotional development issues, Child behavior issues, Adolescent mental health issues, Adolescent behavior issues (Stein, Gentile, Herba, Kingston)

concern are the gaps in evidence – WHO reports that maternal mental health data exist for 90% of HICs yet only 10% of LMICs[20]. Health resources in LMICs are stretched and most have a dearth of mental health professionals and services[19,21]. Further, women in LMICs may be at higher risk for perinatal depression due to high lifetime fertility[22]. The ten countries with the highest total fertility (6-8 children per woman) are located in the African Region, thus women in this region spend much of their reproductive years in pregnant or postpartum states – times of high risk for depression[22].

Manifestation and trajectory of maternal depression has not been adequately researched. Existing studies from LMICs are cross-sectional studies with small sample sizes (n<200)[23–29], thus they lack generalizability and information about temporal changes to adequately inform targeted intervention. Comprehensive evaluation of the manifestation and trajectory of depression among adolescents and adults throughout the entire pregnancy and postpartum periods is necessary to inform future intervention tailored to these populations, especially in LMICs where most young pregnancies take place globally. Effectiveness of such interventions can be optimized in real-world settings thorough identification of the specific depressive symptoms, predictors, and severity unique to pregnancy, early postpartum, and late postpartum periods.

Links between maternal depression, adolescence, and poor neonatal health are well-established. Associations between a mother's well-being and her infant's health have been found across varied contexts.[30–33] A meta-analysis from 2010 combining data from HICs and LMICs found an association between depression during pregnancy and both preterm birth and low birthweight[33], while another in 2013 confirmed the influence of maternal depression on preterm birth[32]. One meta-analysis among LMICs points to a relationship between maternal depression (assessed during and after pregnancy) and stunting (pooled OR: 1.4, 95% CI: 1.2 – 1.8).[34] Few studies have examined associations between maternal depression and adverse

perinatal outcomes in SSA, and existing evidence from this region is mixed (Nigeria[35], Malawi[36], Ethiopia[37], and South Africa[38]). The present study offers a unique opportunity to expand the evidence-base by leveraging data from a large (N>4000) cohort with sufficient power to detect relationships between maternal depressive symptoms and rare perinatal outcomes. Stronger evidence for the interconnectedness of a mother's mental health and her infant's wellbeing will motivate attention toward addressing mental health in African settings where resources are spread thin and mental health services are lacking.

The majority of health system contacts made during the perinatal period in sub-Saharan Africa occur within maternal and child health (MCH) clinics, offering a high-impact access point for perinatal depression screening, yet guidelines for selecting perinatal depression screening tools for use in these settings are lacking. **Screening instruments that effectively identify individuals who would benefit from focused monitoring and intervention will be increasingly important as LMICs adopt policies promoting maternal mental health.[39–43]**

Chapter 2: Is there an optimal screening tool for identifying perinatal depression within clinical settings of sub-Saharan Africa?

In approaching population-level screening for any disorder, important clinical, ethical, and logistical trade-offs must be considered.[44,45] Foremost, health services should be available to slow disease progression or treat the disorder if widespread detection is recommended.[44,45] In LMICs with inadequate resources for mental health, screening for depressive symptoms during maternal child health care may pose undue burden on expectant mothers if next steps for treating their depression are unavailable. Further, a suitable screening test should be available which is reasonably inexpensive, feasible to administer, acceptable to the population being screened, reliable in its measurement, and which optimizes detection of true disease (sensitivity) and absence of disease (specificity).[39] A host of tools exist for depressive symptom screening fitting this description[46–48], however their vast number and heterogeneous performance across populations[46–49] pose additional quandaries for tool selection.

A few screening tools exist that detect depressive symptoms as they specifically manifest during the peripartum period[47], such as the commonly used Edinburgh Postnatal Depression Scale (EPDS).[50,51] Despite the inclusion of "postnatal" in its name, the EPDS is also validated for use antenatally.[52] General depression screening tools are also frequently applied within pregnant and postpartum populations[40,47], even though evidence for their utility during this period has not been extensively explored.[40] The US Preventive Services Task Force (USPSTF) – a "think tank" of primary care and public health experts – recently undertook a systematic review of screening approaches for peripartum depression, ultimately highlighting direct and indirect benefits of screening even when it does not motivate treatment.[46] This report focused on illuminating the validity of the EPDS as the most commonly used peripartum depression instrument, citing thin evidence for the accuracy of the Patient Health Questionnaire (PHQ) (perhaps the most frequently used general depression screening instrument) for pregnant and postpartum women.[46] Despite this finding, a diverse range of screening tools continue to be utilized globally for peripartum screening[39–41,43,53], obfuscating the decision for which tool is truly optimal for use in high-burden settings of sub-Saharan Africa.

In Chapter 2, we synthesize evidence depicting relative strength (low, medium, high) of perinatal depression screening scales for use among African pregnant and postpartum women within four quadrants: 1) diagnostic performance, 2) cultural adaptation, 3) feasibility and ease of implementation, 4) evidence-base from SSA settings.

Chapter 3:
Comparing depression screening tools (CESD-10, EPDS, PHQ-9, and PHQ-2) for diagnostic performance and epidemiologic associations among postpartum Kenyan women

Systematic reviews and meta-analyses by Dadi and colleagues (2020), Chorwe-Sungani et al (2017), Gelaye et al (2016), and Tsai et al (2013) highlight varied depression screening tools utilized within maternal and child health settings yet do not directly compare them to inform prioritization. Tsai and colleagues estimated pooled diagnostic performance metrics (e.g.,

sensitivity and specificity) for the Edinburgh Postnatal Depression Scale but did not compare this tool to other tools. Depression screening tools have not been compared for other influential characteristics such as associations with known cofactors or diagnostic yield which are relevant for research and practice. Empirical comparison of the most widely used depression screening scales in large cohorts can provide important data to inform scale selection for wide programmatic use and integration.

Extending our evaluation of the current evidence-base for depression screening tool performance among perinatal African women, we performed the first study to compare four commonly used perinatal depression screening scales for a range of performance characteristics in a large multi-site cohort of Kenyan women. In Chapter 3, we compared the Edinburgh Postnatal Depression Scale (EPDS), Patient Health Questionnaire-9 (PHQ-9), Patient Health Questionnaire-2 (PHQ-2), and Center for Epidemiologic Studies Depression Scale (CESD-10) for diagnostic yield, symptomatologies, detection of epidemiologic associations with known cofactors of perinatal depression, and diagnostic performance to detect depression. Our results highlight tradeoffs for tool selection with implications for research and practice.

Chapter 4:
Trajectories and predictors of perinatal depressive symptoms among Kenyan women

Since all social, behavioral, and physiological conditions evolve over time, our capacity to accurately depict the prospective development of such outcomes as they concern human health is paramount to our understanding and, ultimately, intervention against adverse conditions.[54] Statistical methods to describe and analyze longitudinal, time-based data provide the empirical foundation for our comprehension of disease trajectory. The power of trajectory modeling lies not only in plotting the population average experience and individual variability about the mean, but in further distinguishing the experiences of unique sub-groups that follow distinct patterns based on a network of characteristics.

Conventional methods succeed in portraying group-level course based on known, measured attributes such as gender or age category.[55] Advancing this descriptive capability, contemporary methods such as trajectory analyses utilize a data-driven, iterative approach to illuminating innate, unmeasured groups underlying the population average trajectory to discern unique disease courses and prioritize individuals for intervention informed by these patterns.[54,56] Well-identified yet poorly understood conditions, such as depression affecting pregnant and postpartum women, are suitable for evaluation with such methods. While application of trajectory modelling inspired advancements in peripartum depression research over the past decade, studies have predominantly taken place within high-income settings.[57,58] Only three perinatal depression trajectory analyses from the African region have been conducted to date, all in South Africa.[59–61] Addressing maternal mental health globally necessitates extension of trajectory modelling to as yet underprioritized peripartum populations. Further application of these models within sub-Saharan African peripartum populations will help prioritize groups for treatment with the highest risk and burden of depression within contexts of limited mental health resources.

In Chapter 4, to our knowledge, our team performed the first perinatal depressive symptoms trajectory analysis in a LMIC setting that involved evaluation of time-varying correlates. East Africa is a setting with rapid momentum for integrating mental health services into maternal child health, yet this is the first assessment of trajectories of perinatal depressive symptom in the region.

Chapter 5:
Perinatal depression and correlates among Kenyan women living with HIV

Risk of perinatal depression is 50% higher among women living with HIV (WLWH),[62–64] likely due to stress about vertical transmission, HIV-related stigma, and the compounding psychosocial impacts of concurrent HIV-infection and motherhood.[65–67] Perinatal depression may reduce vigilance with HIV prevention behaviors[68] and adherence to antiretroviral therapy among WLWH, influencing adverse HIV outcomes.[69] Despite the exacerbating effects of perinatal

depression and HIV, alarming gaps exist in understanding the predictors and patterns of perinatal depressive symptoms among women living with HIV. The World Health Organization recommends expanding access by integrating mental health services into programs with high patient attendance such as maternal child health and prevention of maternal-to-child transmission of HIV (PMTCT) programs. Solutions integrated in MCH or PMTCT services could have high impact in sub-Saharan Africa where prevalence of perinatal depression is high,[70] MCH/PMTCT is well-attended, and a range of evidence-based interventions effectively alleviate perinatal depression.[71–76] Identifying correlates of depression in pregnancy, longitudinal patterns of depressive symptoms, and predictors of trajectory group membership would inform WLWH to prioritize for mental health services in MCH/PMTCT.

In Chapter 5, we performed two evaluations among a cohort of Kenyan women living with HIV enrolled in the Mobile WAChX study--a randomized controlled trial conducted at 6 MCH clinics in the Nairobi and Nyanza regions of Kenya (clinical trial NCT02400671).[77] The first, Chapter 5a, we aimed to understand which WLWH are most at-risk for depression in pregnancy, as well as the magnitude of influence of associated correlates, thus we estimated the prevalence and cofactors of depression during pregnancy and the population attributable risk percent among this population. In Chapter 5b, we identified trajectories and predictors of postpartum depression among WLWH followed through 24 months postpartum to further inform efficient mental health resource allocation within PMTCT programs.

Chapter 6:
Maternal depressive symptoms increase risk for pregnancy loss, preterm birth, and low birthweight among Kenyan mother-infant pairs

Experiencing depression during pregnancy is as common[19,78,79], if not more so than postpartum depression, despite prior notions that pregnancy offered protection against depressive symptoms.[14,32] About 10% of women worldwide are depressed during pregnancy, and the burden is even higher in low- and middle-income countries where 25% of childbearing women suffer from depression.[19,42] Changes in reproductive and stress hormones induced by gestation,

as well as innate genetic factors influence occurrence of maternal depression, yet their specific processes are not fully determined.[80] Depressive symptoms during pregnancy are also impacted by prior adverse life experiences, history of depression or anxiety, lack of social support, issues with a partner such as experience of violence, among other sources of stress.[13,81–84]

Unfavorable outcomes[85] for the mother herself, her infant, and for their relationship together occur across a wide spectrum of harms with potentially long-lasting effects.[81,86,87] The outcome of greatest risk to the mother is postpartum depression--half of those identified as depressed after delivery actually experienced it during or prior to pregnancy.[32,88] The gamut of outcomes hypothesized or known to stem from affective disorder during pregnancy include maternal suicide, perinatal outcomes (e.g., preterm birth, low birthweight, and small for gestational age), late breastfeeding, infant death, suboptimal infant growth, and infant, child, and even adolescent behavioral and mental health problems.[87] Mechanisms linking maternal mental disorder to these diverse consequences are largely unknown[81], and the strength of evidence varies dramatically. Furthermore, these relationships are understudied in sub-Saharan Africa – the region with the highest burden of adverse perinatal outcomes globally.

In Chapter 6, we evaluated potential relationships between multiple psychosocial factors (depression, low social support, intimate partner violence) and multiple adverse perinatal outcomes (pregnancy loss, stillbirth, preterm birth, low birthweight, small-for-gestational age, and neonatal death) among a large cohort of Kenyan women. To our knowledge, this is the largest study to assess maternal mental health and its relationship to over three birth outcomes among mothers and infants in Africa.

Summary

This dissertation aims to advance understanding of the manifestation and patterns of maternal depression among Kenyan women throughout pregnancy and postpartum periods, and to estimate relationships between maternal depression and adverse perinatal outcomes. Our work provides robust evidence about the burden of perinatal depression in this population, as well as important changes throughout the perinatal period. We also identify correlative factors that prioritize women for mental health services and inform effective intervention. Ultimately, we quantify the impact of depression during pregnancy on risk of a range of adverse perinatal outcomes, with the goal of understanding how alleviation of maternal depression could improve neonatal health and survival. Altogether, these results highlight the need for integrated mental health, maternal child health, and HIV prevention and treatment services to alleviate maternal mental distress and linked maternal-infant health outcomes to promote dyadic well-being.

Chapter 2:
Is there an optimal screening tool for identifying perinatal depression within clinical settings of sub-Saharan Africa?

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Is there an optimal screening tool for identifying perinatal depression within clinical settings of sub-Saharan Africa?

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ABSTRACT

Depression is a leading cause of maternal morbidity and mortality worldwide and the most common complication of the perinatal period. Women in sub-Saharan Africa (SSA) are disproportionately impacted by perinatal depression. Maternal and child health (MCH) clinics are widely attended in SSA, offering a potential access point for depression screening. Yet, selection of optimal depression screening instruments for use within MCH clinics in SSA remains unclear. We synthesized evidence depicting relative strength of perinatal depression screening scales for use among African perinatal women within four evaluation domains: 1) diagnostic performance, 2) cultural adaptation, 3) feasibility and ease of implementation, 4) experience using the tool in SSA perinatal populations. The Edinburgh Postnatal Depression Scale (EPDS) and Patient Health Questionnaire-9 (PHQ-9) had the most evidence among peripartum women in SSA, and a balance of feasibility, diagnostic performance metrics, and cultural adaptations. Other depressive screening instruments developed for general populations show strengths for application in African perinatal populations in at least one evaluation domain. Building health services capacity to integrate depression screening within routine MCH visits is an important next step to address perinatal depression in SSA.

Keywords: perinatal, depression, sub-Saharan Africa, screening, mental health, pregnancy, postpartum, Edinburgh Postnatal Depression Scale, Patient Health Questionnaire-9

INTRODUCTION

Depression is a leading cause of disability worldwide, affecting women twice as frequently as men [6,89]. Depression during pregnancy and the first year postpartum is the most common complication of the perinatal period [78,90], and disproportionately affects women in low- and middle-income countries (LMICs) [19,78]. A wide spectrum of adverse outcomes may follow maternal depression [90], including maternal suicide, adverse perinatal outcomes, difficulties in bonding, and infant-child-adolescent developmental problems.

There is growing advocacy for integrating depression screening into Maternal Child Health (MCH) services [91] especially in sub-Saharan Africa (SSA) where MCH services are widely attended and offer a high-impact access point for other health domains [91,92]. While there are multiple depression screening tools available, it is unclear which are optimal for wide-scale implementation in SSA MCH clinics. We summarized findings from the literature to date, highlighting aspects relevant for prioritizing tool selection for this population. We focused on the following characteristics of screening tools used to detect perinatal depression in SSA: diagnostic performance of screening instruments, cultural adaptation, feasibility of implementation within real-world MCH services [93], and experience using the tool in SSA perinatal populations. We summarized our findings across these four evaluation domains per screening tool and overall to depict relative strength of screening tools in each domain. This is the first evaluation to extend assessment of perinatal depression tools beyond diagnostic validity to include important characteristics for programmatic implementation in SSA settings.

CONSIDERATIONS FOR PERINATAL DEPRESSION SCREENING IN SUB-SAHARAN AFRICA

General considerations for disease screening

In approaching population-level disease screening, it is important to consider clinical, ethical, financial, logistical, and human resource issues. Foremost, health services should be

available to manage the disorder if widespread screening is recommended. In clinical settings with inadequate resources for mental health services, screening for depressive symptoms during antenatal and postpartum care may be considered unethical if next steps for adequately managing clinically significant symptoms are difficult to access. Mental health treatment options such as lay counselor-delivered psychosocial interventions are increasingly available in SSA settings, further encouraging the identification of optimal screening tools [76]. A suitable screening tool should be low cost to the health system, feasible to administer, acceptable to the population being screened, valid, and reliable in its measurement [39].

Screening for depression among perinatal women

During the perinatal period, the health of mothers and infants is intrinsically linked. Poor maternal mental health adversely affects the dyad [90], making identification of perinatal depression crucial for both mother and infant health. Women interface with the health system and community-based care more frequently during the perinatal period than other life periods, presenting a unique opportunity for widespread symptom ascertainment [94].

Some expert groups such as the US Preventive Services Task Force and American College of Obstetricians and Gynecologists recommend universal depression screening at least once during the perinatal period [46,95]. They base this guidance on the frequency of depression among perinatal populations and cite evidence of moderate direct or indirect mental health benefits among populations undergoing screening [46,95]. Experts in Canada and United Kingdom assert that there is insufficient high-quality data to support population-level resource allocation toward perinatal depression screening. They suggest that widespread perinatal depression screening may cause more harm than benefit through overtreatment of those receiving falsely positive screening results [96–98]. Experts in the US and elsewhere counter that providing mental health services to those screening positive for perinatal depression (even false positives) may incite more benefit than harm, particularly in settings offering psychosocial support or other non-pharmaceutical treatment options [46,95].

In parallel to this debate, depression is gaining attention as an urgent global public health issue in expert-led clinical intervention programs, global development agendas, and donor-led initiatives for research priorities such as the World Health Organization Mental Health Gap Action Programme (WHO mhGAP) [99], the United Nations Sustainable Development Goals [100], and the Grand Challenges in Global Mental Health, respectively [4]. These initiatives call for worldwide prioritization of case identification for mental disorders within routine primary and community care settings [4,91].

As more settings adopt policies promoting maternal mental health, it is important to understand which screening instruments appropriately identify individuals for monitoring and intervention within specific populations [39–43]. A few screening tools are tailored to assess depressive symptoms during the perinatal period, including the Edinburgh Postnatal Depression Scale (EPDS) [101], which is also validated for use during pregnancy [52]. General depression screening tools are also applied within perinatal populations [40], including those in SSA, though evidence for their utility during these periods has not been extensively evaluated [39–43] (Table 2.1, Figure 2.1).

Screening for depression among perinatal women in sub-Saharan Africa

Some SSA countries maintain specific guidelines for mental health screening, such as South Africa's *National Mental Health Policy Framework and Strategic Plan: 2013-2020* [102] which recommends routine screening for mental illness during pregnancy, and the *Kenya Mental Health Policy: 2015-2030* [103] which recommends increased mental health screening generally. However, mental health screening is not routinely integrated in MCH clinics in SSA and depression screening for perinatal populations remains controversial [104]. In SSA, most health system contacts made during the perinatal period occur within outpatient settings, including MCH clinics (e.g., well-child visits, infant immunization visits). Guidelines for operationalizing programmatic depression screening, care, and referral within MCH are lacking.

CONSIDERATIONS FOR PRIORITIZING A PERINATAL DEPRESSION SCREENING TOOL IN SUB-SAHARAN AFRICA

Depression screening tools have been assessed using systematic reviews, comparative studies, and meta-analyses, predominantly comparing scales for diagnostic performance metrics (e.g., sensitivity, specificity) [39–43,46]. In a purposive literature search using PubMed and snowball searching [105], we identified five systematic reviews synthesizing data on performance of screening tools among perinatal populations across LMICs [39,42,43,106]; one specifically in SSA [40]. The most recent systematic review (Chorwe-Sungani et al., 2017) [39] included studies published through 2015. We conducted a PubMed search (Appendix 1. PubMed Search Terms) to identify studies on this topic published from January 2015 through July 2021. From 57 results returned, we identified 11 additional articles relevant to developing or assessing performance of depression screening tools among perinatal populations in SSA [107–117]. Systematic reviews and articles were included in our narrative review if they reported characteristics of depression screening tool validity (either construct, content, face, or criterion validity) among perinatal populations in SSA. Studies and reviews evaluating diagnostic performance (criterion validity) compared depressive screening tools against clinical diagnostic interview as the reference standard. These studies and reviews discuss the importance of linguistic and cultural adaptation for accurate measurement [39,106]. Unfortunately, there is no standardized approach for evaluating a tool for these characteristics, thus our narrative synthesis discusses findings from heterogeneous studies.

Challenges for perinatal depression screening in resource-limited clinical settings include high patient volumes and busy healthcare workers who cannot dedicate more than a few minutes to each patient [91,92]. Task-shifting models where non-specialized healthcare workers and lay counselors perform perinatal depression screening have been recommended and tested in these settings [94,118]. These studies found adequate performance by non-specialized counselors in delivering mental health screening and services, offering a scalable solution [94,118]. Further, the rich diversity of ethnic groups and languages in SSA necessitates multiple linguistically-tailored

screening tools with associated provider training [106]. Acceptability for publicly discussing mental health varies, and MCH clinics may not have available private rooms for confidential interviews, causing discomfort to patients [106]. Comorbidities such as HIV infection may increase the complexity of depression screening [106].

Despite these barriers, perinatal depression screening may be particularly impactful in SSA where the prevalence of depression is high, where MCH services are the most well-attended health services in the region, and where affordable, sustainable interventions for depression are effective [76,119]. Attention to multiple factors is needed when selecting a screening tool for perinatal populations in resource-limited settings.

We focus on diagnostic performance, cultural adaptations, feasibility, and use in MCH clinics in SSA to evaluate perinatal depression screening tools. We summarized our findings across these four evaluation domains per screening tool (Table 2.1) and overall to depict relative strength (high, medium, low) of screening tools in each domain (Figure 2.1). Categorization of strength level per evaluation domain was determined by the authors according to agreed-upon criteria (Table 1). We placed each depression screening tool into quadrants defined by the evaluation domains according to strength level to visually synthesize results (Figure 2.1).

Screening instrument diagnostic performance

A screening tool's diagnostic performance to balance accurate identification of cases (sensitivity) with valid identification of non-cases (specificity) when compared against a clinical diagnosis is a key feature to consider in selecting a screening instrument. High sensitivity ensures those with depression who would benefit from referral to additional mental health services are not missed due to a false negative result. Concurrently, specificity should be optimized to reduce misallocation of provider time to those with a false positive screening result. In high-resource settings where screening tests are the initial step in directing patients toward further diagnostics by a specialist[46] tools that cast a wider net (more sensitive, less specific) are permissible since resources exist over multiple care stages to distinguish cases from false positives. In clinical

settings worldwide which rely on task-shifting for mental health screening and service provision, the ideal balance between sensitivity and specificity for these settings may be influenced by the referral process, costs, and accessibility. Higher specificity may be useful for resource allocation at the cost of sensitivity loss in such settings.

Tsai and colleagues demonstrated that using the same cut-off, sensitivity and specificity of the EPDS differed between perinatal women in SSA and those in the United States/Europe. In their pooled estimates of sensitivity and specificity of the EPDS compared to diagnostic interview in 14 studies among African perinatal populations, the cut-point score of ≥12 (applied in Western settings as the level optimizing sensitivity and specificity) was associated with higher specificity and lower sensitivity among African perinatal women (68% sensitivity, 93% specificity) [40]. A lower cut-point of ≥10 produced equivalent diagnostic performance metrics (>80% sensitivity/specificity) to the standard higher cut-points of ≥12 or ≥13 among Western groups [40,46]. Programmatic considerations could be incorporated to choose relevant cut-points for use in the diverse communities and contexts of SSA MCH. If programs desire higher specificity and lower sensitivity to decrease unnecessary referrals, the higher cut-point may be useful.

From their systematic review of 26 studies evaluating various depressive screening tools among African perinatal populations, Tsai and colleagues noted that the EPDS was the only scale assessed for all of the following metrics: criterion-related validity (14 studies), reliability (12 studies), construct validity (6 studies), and content validity (5 studies) [40]. These researchers concluded that the EPDS is acceptably valid for use in SSA [40].

This review identified other scales far less frequently applied among perinatal populations with insufficient data for pooled diagnostic performance metrics (Beck Depression Index [BDI], Kessler Psychological Distress Scale-10/-16 [K-10/K-16], Hopkins Symptoms Checklist 25 [HSCL], General Health Questionnaire [GHQ]) [40]. Chorwe-Sungani et al. synthesized diagnostic performance metrics for tools used across LMICs for perinatal depression, similarly finding the EPDS had high sensitivity and specificity (>85%) [39]. Other screening tools assessed by Chorwe-

Sungani et al. were used far less frequently (if at all) in African settings, and had lower accuracy than the EPDS [39]. These reviews highlight the importance of evaluating diagnostic performance of a screening tool in the relevant context to ensure appropriate cut-points and understand the tool's performance [39–43].

Results from individual diagnostic performance studies included in these reviews offer preliminary support for the criterion validity of the Patient Health Questionnaire (PHQ-9) (cutoff ≥9: 94% sensitivity, 75% specificity),[120] Hospital Anxiety and Depression Scale (93% sensitivity, 91% specificity) [121], and potentially the GHC, CES-D, HSCL which showed lower but acceptable sensitivity and specificity in a few studies among African perinatal women [39,40,106,117] (Table 2.1, Figure 2.1).

Future analyses of depression scale validity among perinatal populations of SSA should evaluate psychometrics beyond sensitivity/specificity such as reliability, content, and construct validity to inform tool prioritization across numerous scales.

Cultural appropriateness, acceptability, and adaptation of tools

Relevance of a screening tool for identifying depression within cultural constructs of mental health in a specific region is important. Incorrect interpretation of a question or its answer leads to inaccurate endorsement of items which could eventually produce an incorrect screening result. In the context of pregnancy and postpartum, specific cultural expectations of symptoms such as fatigue or appetite may influence assessment of depressive symptoms [106,122]. Sweetland and colleagues examined the consequences of inappropriate adaptation of depressive symptom screening tools in their systematic review of qualitative interviews from diverse settings in 16 SSA countries where participants were asked to "think aloud" as they responded during screening assessments [106]. These authors summarize findings about appropriateness of depression screening tools for African populations (including perinatal women) into thematic areas of "linguistic", "conceptual", and "content/factorial validity" [106].

Misunderstandings often stemmed from linguistically inappropriate portrayals of "depression" within different cultural contexts. For instance respondents in Eritrea and South Africa reported depression using idioms such as "thinking too much", "sighing", or "the heart is sore", among others [106]. A study specifically examining local idioms of perinatal depression in South Africa additionally found common phrases of "stress", "being sad or unhappy", or "being scared" as common symptoms-based descriptions of depression [123]. Others used metaphors evoking a depressed state such as "you feel the sun has set even though it's morning", "you don't feel like yourself even when you are walking", and "you are like the weather" [123]. These authors concluded that it was important to elicit locally-relevant descriptions of perinatal depression. Further, symptoms identified via local idioms aligned well with international diagnostic criteria from the DSM-5 and ICD-10 when accurate translations were used and interviews were conducted by trained individuals [123].

Specific screening scale items may cause confusion as highlighted by Sweetland et al. For instance, questions about changes in appetite within the PHQ-9 were perceived in African settings to be asking about food insecurity [106]. Discussions across the literature challenge the appropriateness of using screening instruments that rely on somatic symptoms within perinatal populations since changes in appetite, weight, sleep, and fatigue are natural components of the perinatal period – they may not indicate depression [101,124]. This inspired the original development of the EPDS and continues to motivate its use [101,124].

In a recent publication detailing the process of translating the EPDS questionnaire for Kiswahili-speaking communities, Kumar and colleagues implement four criteria for achieving linguistic equivalence [125]. These are: informativeness, source language transparency, security, and practicality – steps which allow multiple researchers to collaboratively adapt the tool for context-specific appropriateness [125]. Those aiming to apply a perinatal depression screening instrument to a setting which lacks an adapted version should engage in similar procedures to enhance scale performance. Conducting cognitive interviews can illuminate how respondents

understand and interpret survey questions developed within a different population, highlighting areas for adaptation [107,126,127]. Velloza and colleagues performed cognitive interviews among perinatal women in Kenya to evaluate comprehension of the PHQ-9, finding that respondents had difficulty answering double-barreled questions and items concerning circumstances not relevant to their lives (e.g., "watching television") [107]. Further, a multi-stage process involving mixed methods to comprehensively adapt a depression screening tool for use in a new setting may be necessary, such as the development and evaluation process used for the novel Shona Symptom Questionnaire in Zimbabwe [128]. More recent efforts follow similar multi-stage processes to adapt depression scales for use among specific perinatal populations in SSA [108,109,111,116,129], including Davies and colleagues' development of a version of the Hamilton Depression Rating Scale for use by non-clinicians in South African perinatal populations [110], and the Green et al. process to develop and validate a perinatal depression screening tool involving local idioms in Kenya [115].

When selecting a screening tool for detecting perinatal depression in SSA clinical settings, culturally adapted scales that have been modified to achieve linguistic-conceptual equivalence should be prioritized. The EPDS and PHQ-9 have been culturally adapted for perinatal populations in multiple African countries. The Shona Symptom questionnaire (SSQ) is the first published indigenous mental health screening scale developed for groups in SSA using ethnographic, qualitative input and was validated in perinatal women (Table 2.1, Figure 2.1) [130].

If adapted versions of scales are not publicly available for use in a specific setting or population, efforts to adapt the scale for language, context, and conceptual relevance should be initiated. At a minimum, findings from non-adapted scales applied to perinatal depression screening should be interpreted cautiously with ample discussion of limitations.

Feasibility and ease of implementation

In the context of busy clinics with high patient-to-provider ratios and few-to-no mental health specialists, ease of implementation is an essential factor when selecting a screening tool for perinatal depression [39]. In their review of tools used in LMICs which included long-form and

brief formats, Akena and colleagues found short scales were as effective as longer ones in identifying perinatal depression [41]. Cultural and linguistic appropriateness facilitates implementation since confusing language hinders efficient administration. For example, qualitative interviews in Ethiopia revealed that use of the phrase "for no good reason" in the EPDS impeded ease of use [106].

Question structure negatively affected accuracy of responses in Sweetland's assessment; specifically double-barreled and long-winded questions performed poorly (e.g., "do you ever hear voices without knowing where they are coming from or which other people cannot hear?" from the Self-Reporting Questionnaire) [106]. Instruments using bidirectional questioning with some questions phrased positively and others negatively also caused confusion (e.g., EPDS, PHQ-9, GHQ, and others) [106]. These authors highlight findings from two Kenyan studies where application of Likert scale items (e.g., "a little" vs "quite a bit") and the two-week reference period for PHQ-9 responses as a proportion of days (e.g., "more than half the days") adversely affected accuracy of responses [106].

In their assessment of eight common depression screening tools for perinatal depression among South African women, van Heyningen and colleagues suggest that short (4-item), binary-scoring tools such as Whooley questions may be easier to implement in busy, resource-limited health settings than longer, Likert scale instruments [131]. A recent evaluation of the Whooley questions compared to the EPDS among South African perinatal women found that the Whooley questions had the advantage of brevity and simplicity, while maintaining high diagnostic performance [112]. Akena et al. agree that, "brief scales may have an edge over the longer instruments" [41]. Depressive symptom scales applied to African perinatal populations to date ranged from two items (PHQ-2) to 60 items (GHQ-60), nearly all use Likert-style response options, and most use bidirectional questioning (Table 2.1, Figure 2.1). The Shona Symptom Questionnaire and Self-Regulation Questionnaire have high ease of implementation as brief instruments (<25-items) with binary responses and unidirectional question format (Table 2.1).

Other considerations for feasibility include self-administration versus clinician-administration of tools [40,106]. To date, the global dialogue surrounding expanded screening for perinatal depression in LMICs focuses on task-shifting depression screening from specialized mental health providers to non-specialized clinicians and community health workers to improve access [91–93]. The relative complexity of depression screening instruments should be considered in task-shifting and self-administration scenarios to optimize accuracy of results.

Experience with use among African perinatal populations

Experience using a screening tool within clinical settings may offer advantages, when combined with adequate diagnostic performance, cultural adaptation, and implementation feasibility [132]. In selecting a depression screening instrument, the "degree of uptake by other practitioners and healthcare systems" should be considered in concert with performance characteristics, as widespread understanding of questions and scoring across clinical settings facilitates consistent administration and interpretation [132,133]. From the ten different perinatal depression screening tools identified by Tsai and colleagues as being applied within perinatal populations in their systematic review of screening in Africa, the EPDS surfaced as the most frequently used instrument which is consistent with utilization in settings globally [40]. They state that, "while other standard instruments could, with limitations, be employed to screen for perinatal depression,…the weak evidence base is a major barrier to sound programming" [40]. Frequency of use strengthens support for utilizing the EPDS in African clinical settings. The PHQ-9 and GHQ are the next most frequently used depressive screening tools among African perinatal populations within the literature to date (Table 2.1, Figure 2.1). The PHQ-9 has been integrated into HIV care settings in multiple countries of SSA [134] including programs involving perinatal women, potentially strengthening the case for wider-scale use of the PHQ-9 for perinatal depression screening in SSA.

While the EPDS had the highest relative frequency of use, it is worth noting that depressive symptom screening is generally *infrequent* across community, public, and private sector health

facilities in sub-Saharan Africa. Familiarity with screening tools among healthcare workers and patients is relatively low and may not have reached a threshold to prioritize any specific screening tool over another based-on commonality of use. Existing evidence of depression screening tool use in perinatal populations in SSA is from research, as opposed to routine clinical settings.

IMPLICATIONS FOR WIDESPREAD PERINATAL DEPRESSION SCREENING IN SSA

The specific challenges and opportunities for perinatal depression screening in African MCH clinics make it critical to select the most appropriate screening tool carefully. Busy and resource-limited clinical settings require a screening instrument that is easy to implement, well-understood by the population, and accurate in classification. Simple, short instruments which maintain accurate identification of cases may be more appropriate in contexts of task-shifting or self-administration within MCH clinical settings of sub-Saharan Africa.

Overall, the EPDS and PHQ-9 tools have higher performance characteristics and frequency of use among SSA perinatal populations that support implementation in MCH settings compared to other instruments. Other tools are less well-studied but show strengths in at least one evaluation domain for application in African perinatal populations, inspiring further investigation. All tools evaluated (including the EPDS and PHQ-9) have shortcomings necessitating careful adaptation for specific perinatal populations and thoughtful interpretation of results. Future research should focus on comprehensively adapting existing tools to ensure high performance across the four evaluation domains. A similar evaluation of existing screening tools for other prevalent perinatal mental disorders such as, anxiety and post-traumatic stress, is also urgently needed. Implementation science strategies will help evaluate approaches to integrating depression screening within MCH visit schedules and assess appropriate timing, potential on-site depression interventions, and referral strategies. Given the high prevalence of depression among peripartum mothers, it remains critical to scale up depression screening in MCH services in SSA to improve maternal and child health and well-being.

Authorship:
AL-conceptualized the idea for the commentary, reviewed articles for the commentary, wrote the first draft, conducted the edits for the drafts, drafted the figure, reviewed and approved final draft. JP-reviewed the data in the figure, reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft. AB- reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft. MK- reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft. JK- reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft. PYC- reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft. GJS- conceptualized the idea for the commentary, reviewed the data in the figure, reviewed all drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft.

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TABLES AND FIGURES

Table 2.1. Assessment of depression screening instruments for application among perinatal populations in sub-Saharan Africa

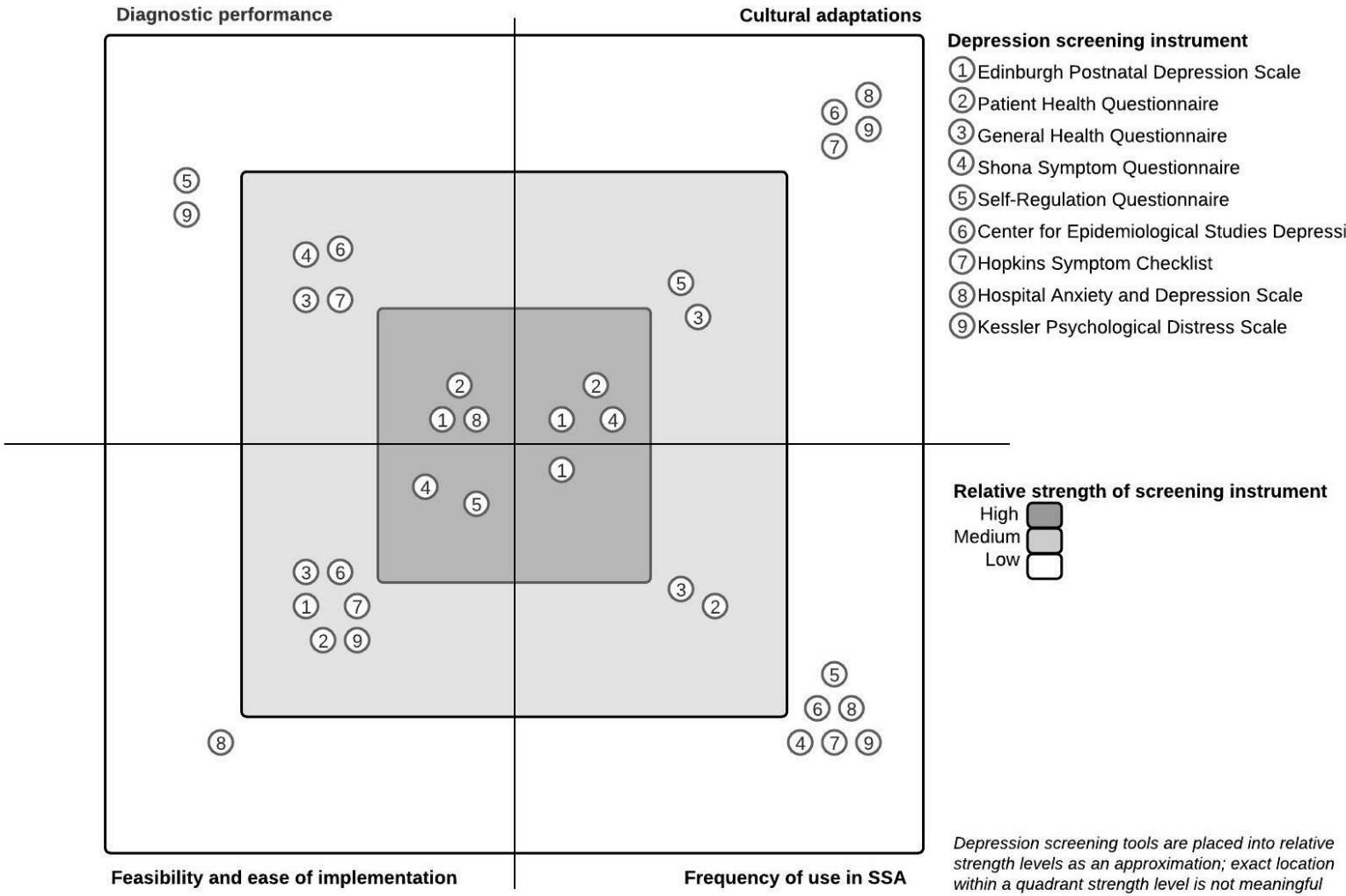
Key: Strength of depression screening instrument High Medium Low

		Diagnostic performance	Cultural adaptations	Feasibility and ease of implementation	Frequency of usein SSA
1	Edinburgh Postnatal Depression Scale (EPDS)	14 studies in SSA with cutoff score ≥9 [40]: Pooled sensitivity: 94%, pooled specificity: 77%	Multiple versions culturally adapted for SSA [43,108,113,125]: Igbo Yoruba Amharic Twi Shona Chichewa Kiswahili	10-items Likert scale responses Bidirectional questions Recall period: "In the past 7 days"	>20 studies among perinatal populations in SSA
2	Patient Health Questionnaire (PHQ)	From one study in Ghana with PHQ-9 cutoff score ≥9 [40,106]: Sensitivity: 94%, Specificity: 75%	Multiple versions culturally adapted for perinatal populations in SSA [39,40,107,116]: Afaan Oromo Kiswahili Kikuyu	10-item, 2-item versions Likert scale responses Unidirectional questions Recall period "Over the past 2 weeks"	>5 studies among perinatal populations in SSA
3	General Health Questionnaire (GHQ)	From one study from Nigeria (GHQ-28) [39,40]: Sensitivity: 82% Specificity: 85%	At least one version culturally adapted for Botswana (not for perinatal populations) [106,135]: Setswana	60-item, 30-item, 28-item, 12-item versions Likert scale responses Bidirectional questions Recall period: "In the past few weeks"	>5 studies among perinatal populations in SSA
4	Shona Symptom Questionnaire (SSQ)	From one study within Zimbabwean pregnant women [39,40]: Sensitivity: 82% Specificity: 66%	First indigenous measure of mental disorder from SSA; validated among perinatal women in Zimbabwe [128,130]: Shona	14-items Yes/No responses Unidirectional questions Recall period: "During the course of the past week"	>1 study among perinatal populations in SSA
5	Self-Regulation Questionnaire (SRQ)	From one study within Ethiopian pregnant women with SRQ-20 cutoff ≥6 [39,40]: Sensitivity: 68% Specificity: 62%	At least one version culturally adapted for Malawian perinatal women [111,136,137]: Chichewa, Chiyao Also translated to: Amharic	20-item scale Yes/No responses Unidirectional questions Recall period: "In the last month"	>1 study among perinatal populations in SSA
6	Center for Epidemiological Studies Depression Scale (CES-D)	From one study in Uganda (CESD-20) [39]: Sensitivity: 73% Specificity:79%	At least one version translated and validated among pregnant women in Uganda [39,138]: Acholi, Langi	20-item, 10-item versions Likert scale responses Bidirectional questions Recall period: "Over the past week"	>1 study among perinatal populations in SSA
7	Hopkins Symptom Checklist (HSCL)	From one study in Tanzania with cutoff [39,40]: Sensitivity: 89% Specificity: 80%	At least one version translated and validated among pregnant women in Tanzania [39,139]: Kiswahili	25-item, 10-item versions Likert scale responses Unidirectional questions Recall period: "In the last 7 days"	>1 study among perinatal populations in SSA
8	Hospital Anxiety and Depression Scale (HADS)	From one study within Nigerian pregnant women [40,106]: Sensitivity: 93% Specificity: 91%	At least one version translated and validated among pregnant women in Nigeria [39,121]: *Language not indicated*	14-items (7-items for anxiety subscale, 7 items for depression subscale) Likert scale responses Bidirectional questions Recall period: questions written in present tense (e.g., "I feel miserable and sad")	>1 study among perinatal populations in SSA
9	Kessler Psychological Distress Scale (K-10/K-6)	From one study within South African pregnant women (K-10) [39,40,106]: Sensitivity: 73% Specificity: 54%	Multiple versions translated and validated for perinatal populations in SSA [39,40,106]: Moore, Dioula, French Afrikaans	10-item, 6-item versions Likert scale responses Unidirectional questions Recall period: "In the past 4 weeks"	>1 study among perinatal populations in SSA

Evidence synthesized from results of systematic reviews: Chorwe-Sungani et al. 2017, Gelaye et al. 2016, Shrestha et al. 2016, Sweetland et al. 2014, Tsai et al. 2013
Diagnostic performance: High = Sensitivity and/or Specificity >90%; Medium = Sensitivity and/or Specificity ≥75%; Low = Sensitivity and/or Specificity <75%
Cultural adaptation: High = Multiple culturally adapted versions available or tool was developed specifically for the population; Medium = One culturally adapted tool identified;

Low = Adaptation of tool is limited to language translation without further cultural adaptation or evaluation
Feasibility and ease of implementation: High = Binary response types, Unidirectional questions, tense of question corresponds to recall period; Medium: Likert scale responses included, bidirectional questions may be included, tense of question corresponds to recall period; Low: Liker scale responses, bidirectional questions, tense of questions does not correspond to recall period (e.g., question phrased in present tense while asking about past experience)
Frequency of use in SSA: High = >20 studies; Medium = 5-20 studies; Low = 1-5 studies

Figure 2.1. Relative strengths of depression screening instruments for application among perinatal populations in sub-Saharan Africa



Diagnostic performance: High = Sensitivity and/or Specificity >90%; Medium = Sensitivity and/or Specificity ≥75%; Low = Sensitivity and/or Specificity <75%
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Frequency of use in SSA: High = >20 studies; Medium = 5-20 studies; Low = 1-5 studies

APPENDIX 1. PUBMED SEARCH TERMS

(Validation OR validity OR validating) AND ("Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR pregnan*[tiab] OR pregnan*[ot])) AND (Depression[tiab] OR Depressive[tiab]) AND ("Africa South of the Sahara"[Mesh] OR "Sub-Saharan Africa"[tiab] OR "SubSaharan Africa"[tiab] OR "sub-Sahara Africa"[tiab] OR "subSahara Africa"[tiab] OR "Sub-Saharan African"[tiab] OR "SubSaharan African"[tiab] OR "sub-Sahara African"[tiab] OR "Africa South of the Sahara"[tiab] OR Angola*[tiab] OR Benin*[tiab] OR Botswana[tiab] OR Burkina Faso[tiab] OR Burkinabe[tiab] OR Burundi[tiab] OR Cameroon*[tiab] OR Cape Verde[tiab] OR "Central Africa"[tiab] OR "Central African"[tiab] OR "Central African Republic"[tiab] OR Chad*[tiab] OR Comoros[tiab] OR Congo*[tiab] OR DRC[tiab] OR Côte d'Ivoire[tiab] OR Ivorian[tiab] OR Djibouti[tiab] OR "East Africa"[tiab] OR "East African"[tiab] OR "Eastern Africa"[tiab] OR "Eastern African"[tiab] OR Equatorial Guinea[tiab] OR Eritrea*[tiab] OR Eswatini[tiab] OR Ethiopia*[tiab] OR Gabon*[tiab] OR Gambia*[tiab] OR Ghana*[tiab] OR Guinea*[tiab] OR Guinea-Bissau[tiab] OR Kenya*[tiab] OR Lesotho[tiab] OR Liberia[tiab] OR Madagascar[tiab] OR Malagasy[tiab] OR Malawi*[tiab] OR Mali[tiab] OR Malian[tiab] OR Mauritania[tiab] OR Mauritius[tiab] OR Mauritian[tiab] OR Mozambique[tiab] OR Mozambican[tiab] OR Namibia*[tiab] OR Niger[tiab] OR Nigeria*[tiab] OR Réunion[tiab] OR Rwanda*[tiab] OR Sao Tome and Principe[tiab] OR Senegal*[tiab] OR Seychelles[tiab] OR Sierra Leone*[tiab] OR Somali*[tiab] OR "South Africa"[tiab] OR "South African"[tiab] OR "Southern Africa"[tiab] OR Sudan[tiab] OR Swaziland[tiab] OR Tanzania*[tiab] OR Togo[tiab] OR Togolese[tiab] OR Uganda*[tiab] OR "West Africa"[tiab] OR "West African"[tiab] OR "Western Africa"[tiab] OR "Western African"[tiab] OR "Western Sahara"[tiab] OR Zambia*[tiab] OR Zimbabwe*[tiab] OR "Sub-Saharan Africa"[ot] OR "SubSaharan Africa"[ot] OR "sub-Sahara Africa"[ot] OR "subSahara Africa"[ot] OR "Sub-Saharan African"[ot] OR "SubSaharan African"[ot] OR "sub-Sahara African"[ot] OR "Africa South of the Sahara"[ot] OR Angola*[ot] OR Benin*[ot] OR Botswana[ot] OR Burkina Faso[ot] OR Burkinabe[ot] OR Burundi[ot] OR Cameroon*[ot] OR Cape Verde[ot] OR "Central Africa"[ot] OR "Central African"[ot] OR "Central African Republic"[ot] OR Chad*[ot] OR Comoros[ot] OR Congo*[ot] OR DRC[ot] OR Côte d'Ivoire[ot] OR Ivorian[ot] OR Djibouti[ot] OR "East Africa"[ot] OR "East African"[ot] OR "Eastern Africa"[ot] OR "Eastern African"[ot] OR Equatorial Guinea[ot] OR Eritrea*[ot] OR Eswatini[ot] OR Ethiopia*[ot] OR Gabon*[ot] OR Gambia*[ot] OR Ghana*[ot] OR Guinea*[ot] OR Guinea-Bissau[ot] OR Kenya*[ot] OR Lesotho[ot] OR Liberia[ot] OR Madagascar[ot] OR Malagasy[ot] OR Malawi*[ot] OR Mali[ot] OR Malian[ot] OR Mauritania[ot] OR Mauritius[ot] OR Mauritian[ot] OR Mozambique[ot] OR Mozambican[ot] OR Namibia*[ot] OR Niger[ot] OR Nigeria*[ot] OR Réunion[ot] OR Rwanda*[ot] OR Sao Tome and Principe[ot] OR Senegal*[ot] OR Seychelles[ot] OR Sierra Leone*[ot] OR Somali*[ot] OR "South Africa"[ot] OR "South African"[ot] OR "Southern Africa"[ot] OR Sudan[ot] OR Swaziland[ot] OR Tanzania*[ot] OR Togo[ot] OR Togolese[ot] OR Uganda*[ot] OR "West Africa"[ot] OR "West African"[ot] OR "Western Africa"[ot] OR "Western African"[ot] OR "Western Sahara"[ot] OR Zambia*[ot] OR Zimbabwe*[ot])

Chapter 3: Comparing depression screening tools (CESD-10, EPDS, PHQ-9, and PHQ-2) for diagnostic performance and epidemiologic associations among postpartum Kenyan women

Submitted for peer-reviewed publication at the time of dissertation completion

Comparing depression screening tools (CESD-10, EPDS, PHQ-9, and PHQ-2) for diagnostic performance and epidemiologic associations among postpartum Kenyan women: Implications for research and practice

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ABSTRACT

Background: Identifying optimal depression screening tools for use in maternal health clinics could improve maternal and infant health. We compared four tools for diagnostic performance and epidemiologic associations.

Methods: This study was nested in a cluster-randomized trial in Kenya. Women in 20 maternal health clinics were evaluated at 6 weeks postpartum with Center for Epidemiologic Studies Depression Scale (CESD-10), Edinburgh Postnatal Depression Scale (EPDS), Patient Health Questionnaire-9 and -2 (PHQ-9, PHQ-2) for moderate-to-severe depressive symptoms (MSD) [CESD-10≥10, EPDS≥13, PHQ-9≥10, or PHQ-2≥3]. We assessed area under the curve (AUC) per scale (CESD-10, EPDS) against probable major depressive disorder (MDD) using the PHQ-9 scoring algorithm. Associations between MSD and intimate partner violence (IPV) were compared between scales.

Results: Among 3605 women, median age was 24 and 10% experienced IPV. Prevalence of MSD symptoms varied by tool: 13% CESD-10, 9% EPDS, 5% PHQ-2, 3% PHQ-9. Compared to probable MDD, the CESD-10 (AUC:0.82) had higher AUC than the EPDS (AUC:0.75). IPV was associated with MSD using all scales: EPDS (RR:2.5, 95%CI:1.7-3.7), PHQ-2 (RR:2.3, 95%CI:1.6-3.4), CESD-10 (RR:1.9, 95%CI:1.2-2.9), PHQ-9 (RR:1.8, 95%CI:0.8-3.8).

Limitations: Our study did not include clinical diagnosis of MDD by a specialized clinician, instead we used provisional diagnosis of probable MDD classified by the PHQ-9 algorithm as a reference standard in diagnostic performance evaluations

Conclusion: Depression screening tools varied in detection of postpartum MSD. The PHQ-2 would prompt fewer referrals and showed strong epidemiologic association with a cofactor.

Keywords: Postpartum depression, Screening, sub-Saharan Africa, CESD-10, EPDS, PHQ-9, PHQ-2

Introduction

Depression is a leading cause of maternal morbidity and mortality during pregnancy and the first year postpartum [78]. It is the most common complication of the perinatal period [90], and disproportionately impacts women in low-income settings [78]. Maternal depressive symptoms during the peripartum period may lead to a wide spectrum of adverse outcomes, including maternal suicide, adverse perinatal outcomes, and potentially child-adolescent behavioral and mental health problems [90].

Integration of depression screening into maternal and child health (MCH) services is increasingly encouraged by initiatives including the World Health Organization Mental Health Gap Action Programme (WHO mhGAP) [99], the United Nations Sustainable Development Goals, and the Grand Challenges in Global Mental Health [4]. These initiatives call for task-shifting to provide case identification and a range of interventions for mental disorders within routine care settings [4,91]. In sub-Saharan Africa (SSA), particularly in Kenya, MCH services are widely attended [140] and offer a high-impact access point for depression screening [91]. MCH clinics may be critical for maternal mental health screening as mental health issues have the potential to amplify other adverse MCH outcomes [90]. However, currently MCH clinics in Kenya and elsewhere in SSA do not routinely offer depression screening and guidelines do not exist for perinatal depression screening in many LMICs. The Kenya Mental Health Policy (2015-2030) commits to increasing mental health service availability across the health system, including MCH, but does not name a preferred screening scale [103].

Multiple depression screening tools are available and utilized within perinatal populations [40,42], yet it is unclear which are optimal for wide-scale deployment among pregnant and postpartum populations in MCH clinics in SSA. The Edinburgh Postnatal Depression Scale (EPDS) [40] is the most commonly used screening scale in perinatal populations in SSA, followed by the Patient Health Questionnaire-9 (PHQ-9) [40] which is increasingly adopted for widescale

depression screening in SSA. Other general depression screening instruments have been utilized in perinatal populations, including the Center for Epidemiologic Studies Depression Scale (CESD-10) [70] and the brief, 2-item version of the Patient Health Questionnaire (PHQ-2) [141]. Prior evaluations of depression screening tools have assessed diagnostic performance metrics (e.g., sensitivity, specificity) [40,42]. However, these varied depression screening tools have not been compared side-by-side for diagnostic performance, associations with known cofactors, and diagnostic yield.

Our study objective was to compare four tools (CESD-10, EPDS, PHQ-9, PHQ-2) commonly used for perinatal depression screening globally for a range of performance characteristics.

Methods

Study setting and population

This analysis was nested in the PrEP implementation for Mothers in Antenatal Care (PrIMA) study, a cluster randomized trial conducted within public sector MCH clinics in Kenya. The PrIMA RCT was designed to compare two models for pre-exposure prophylaxis implementation among pregnant women (NCT03070600) [142]. Participants were enrolled from 20 MCH clinics within Homa Bay and Siaya counties of Western Kenya. Pregnant women were eligible for enrollment if they were HIV-negative, ≥15 years old, and were able to provide consent.

Data collection

Questionnaires were verbally administered by study nurses in Kiswahili, Dholuo, or English languages. This took place in private spaces to ensure confidentiality; participants were not given the option to self-complete depressive screening tools. Participants were surveyed about demographics, pregnancy history, partner characteristics, and psychosocial factors including experience of depressive symptoms. All data collection instruments, including depression screening scales, were formally forward and backward translated from English into

Kiswahili and Dhuluo. The data collection instrument was field tested by study staff and refined as needed.

Depression screening instruments

In this comparative analysis, we evaluated depressive symptoms at the 6-week postpartum visit using four depression screening scales: CESD-10, EPDS, PHQ-9, and PHQ-2. The CESD-10 and EPDS are 10-item screening scales where each item depicts a discrete depressive symptom and participants rate each item between 0 to 3 based on past-week frequency. Higher total scores indicate higher severity of depressive symptoms; scores range from 0-30. Symptoms of moderate-to-severe depression (MSD) was defined as CESD-10 score of ≥10, the validated cut-point [143]. We defined MSD symptoms with the EPDS as a score of ≥13 [144].

Similarly, the PHQ-9 is a 9-item screening scale assessing past two-week frequency of symptoms. Items are rated between 0-3 (range: 0-24); higher scores indicate greater severity. Scores of 10 or greater denote MSD symptoms [145]. The shorter PHQ-2 is comprised of two items: "Little interest or pleasure in doing things" and "Feeling down, depressed, or hopeless". Scores range from 0-6. A cut-point of three or greater denotes likely major depression [145]. Collection of depressive symptom data did not begin at study activation for all scales, thus we do not have data in all scales for all participants.

Diagnostic algorithm for major depressive disorder

Information from the PHQ-9 can be utilized in a scoring algorithm to establish provisional diagnoses for probable major depressive disorder (MDD) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [146,147]. The original validation study of PHQ-9 diagnostic scoring found 85% overall accuracy, 75% sensitivity and 90% specificity compared to physician diagnosis with the DSM-III [147]. An individual is considered to have probable MDD if they responded "more than half of the days" about their experience of at least five items in the past two weeks

and if one these items was “little interest or pleasure in doing things” or “feeling down, depressed, or hopeless” [148]. The item describing suicidal ideation contributes to the criteria at any frequency.

Defining predictors of perinatal depression

Experiencing violence inflicted by an intimate partner during pregnancy is well-established as a strong predictor of postpartum depression [149]. About 2-14% of women worldwide experience intimate partner violence (IPV) which increases risk of postpartum depression by at least two-fold [149]. We examined the strength of association between IPV reported before 6 weeks postpartum and MSD symptoms in postpartum defined by each scale. We assessed IPV using the four-item “Hurt, Insult, Threaten, Scream” (HITS) scale with a cut-point of ≥10 to define IPV (absolute score range: 4-20) [150]. One’s ability to rely on a social network for emotional and logistical support is also associated with postpartum depression [70]. We used the 18-item Medical Outcomes Study Social Support Survey (MOS-SSS) to assess level of social support; participants identify how frequently they find various types of support when needed (higher scores denote higher social support, range: 18-90) [151]. We defined low social support as scores below 72; these participants reported being unable to receive support at least “most of the time” for each scenario [152]. The HITS and MOS-SSS tools are commonly utilized in research studies among populations in SSA [150,153,154]

Statistical analysis

We estimated prevalence of MSD symptoms at 6 weeks postpartum with the CESD-10, EPDS, PHQ-9, and PHQ-2 using descriptive statistics and estimated 95% confidence intervals from standard errors clustered by site. We evaluated differences between each pair of prevalence estimates using McNemar’s tests. Chance-adjusted agreement between scales for their identification of early postpartum MSD symptoms was estimated by Cohen’s kappa coefficients.

Sensitivity, specificity, and area under the curve (AUC) were assessed using receiver operating characteristic (ROC) curves comparing postpartum MSD symptoms for the CESD-10 and EPDS, to probable MDD. We did not compare the PHQ-9 or PHQ-2 screening scores to the

algorithm for probable MDD since comparing summed items to a function of the same items may provide biased diagnostic performance estimates. We evaluated frequency of symptom endorsement for each depression scale among participants identified with MSD symptoms using that scale. To estimate the strength of epidemiologic relationships between IPV (experienced before 6 weeks postpartum), social support (during pregnancy) and postpartum MSD symptoms. we fit generalized linear regression models with binomial family, log link, clustered by facility. Estimates were adjusted for pre-specified confounders (age, marital status, household crowding, and social support or IPV). Analyses were conducted in Stata 15.

Ethical considerations

The study protocol, informed consent forms, and data collection tools were approved by the Kenyatta National Hospital-University of Nairobi Ethics Research Committee and University of Washington Human Subjects Review Committee. All participants provided written informed consent.

Role of funding sources

This work was supported by the National Institute of Allergy and Infectious Disease (R01 AI125498 to GJS), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (F31HD101149 to AL, R01HD100201 to JP and R01 HD094630 to GJS). All grants were externally peer reviewed for scientific quality. The funding agencies had no role in the writing of the manuscript or the decision to submit it for publication.

Results

Population characteristics

The 3,605 study participants who attended both the enrollment and six week postpartum visits and were included in this study. Median age was 24 years (interquartile range [IQR]: 21-29), the vast majority (86%, 3069) married or cohabiting with their partner, and only 8% (284) were currently in school (Table 3.1). About 15% (523) of the women were employed and 10%

(371) experienced household crowding defined as over three people per room in their residence [155]. Median social support score was 76 (IQR: 63-88); 36% (1262) women experienced low social support. One in ten women (10%, 368) reported IPV during pregnancy or early postpartum.

Prevalence of MSD symptoms and agreement between screening scales

Frequency of moderate-to-severe depressive symptoms detected in early postpartum varied by tool. The highest frequency was measured using the CESD-10 where 12.6% (391/3098, 95% confidence interval [CI]: 7.3%-20.8%) of participants had MSD symptoms. The EPDS identified 9.2% (326/3533, 95% CI: 5.9 %-14.2%) of participants as having MSD symptoms. About 4.9% (176/3576, 95% CI: 2.6 %-9.1%) of participants had MSD symptoms with the PHQ-2 and 3.2% had MSD symptoms using the PHQ-9 (74/2328, 95% CI: 1.6%-6.0%). The differences in frequency of MSD symptoms between each pair of scales were statistically significant (p≤0.0 5) (Figure 3.1).

Only 0.6% (13/2328, 95% CI: 0.2%-1.5%) of participants had MSD symptoms in early postpartum in every scale; 17.8% (643/3605, 95% CI: 11.4%-26.8%) had MSD symptoms in at least one scale. There was fair to moderate agreement between tools for classification of MSD symptoms (“Fair”: 0.2 -0.4, “Moderate”: 0.4 -0.6). Between the EPDS and PHQ-2, Cohen’s kappa coefficient was 0.2 20; between the PHQ-9 and EPDS kappa was 0.246, and between the PHQ-9 and CESD-10 it was 0.257. Kappa was 0.269 between the PHQ-2 and CESD-10, 0.369 between the CESD-10 and EPDS, and 0.543 between the PHQ-9 and PHQ-2.

Diagnostic performance compared to MDD

Among those with depressive symptom information in all four scales (n=2328), about 1.7% (n=39, 95% CI: 0.8%-3.4%) had probable MDD in early postpartum using the algorithm to estimate MDD (Figure 3.1). In area under the receiver operating characteristic curve (AUROC) comparisons against probable MDD, the CESD-10 had an AUROC of 0.82; sensitivity 50%, specificity 91% at a score of ≥10. The EPDS had an AUROC of 0.75; 42% sensitivity, 92%

specificity at a score of ≥13. Both scales demonstrated satisfactory diagnostic performance compared to probable MDD classification with the PHQ-9 algorithm (Figure 3.2).

Symptomatology

In our assessment of symptom endorsement among women with MSD symptoms defined by each tool, we found that the three longer scales (CESD-10, EPDS, PHQ-9) identified similar symptoms of feeling overwhelmed ("Everything was an effort" [92%], "Things were getting on top of me" [98%]) or having low energy ("feeling tired or having little energy" [96%]) as the most common among postpartum Kenyan women. A related symptom of anhedonia, or inability to feel pleasure, was the most common symptom reported by those with MSD symptoms defined by the PHQ-2 (92%). The remaining symptoms ranked differently by scale (Figure 3.3).

Detection of associations with known predictor

We found intimate partner violence experienced prior to 6 weeks postpartum was associated with MSD symptoms in early postpartum using each scale. The strength of association varied between scales when symptoms of MSD was defined using the screening thresholds recommended by tool developers. The strongest association was detected by the EPDS where those reporting IPV were 2.5-times more likely to experience MSD symptoms than those not reporting IPV. With the PHQ-2, risk for MSD symptoms among those exposed to IPV was 2.3-times higher than those not exposed. Experiencing IPV put women at 1.9-times higher risk for MSD symptoms in early postpartum with the CESD-10 and 1.8-times higher risk with the PHQ-9 compared to those without IPV. Relationships were robust to adjustment for pre-specified confounders.

Low social support during pregnancy also put women at twice the risk of MSD symptoms in early postpartum as measured with the CESD-10 and 1.5-times higher risk of MSD symptoms measured with the PHQ-2 (Figure 3.4). This relationship was not significant with MSD symptoms in the PHQ-9 or EPDS. Statistical significance was maintained after adjustment for confounders with MSD symptoms in the CESD-10 (p=0.002), yet not the PHQ-2 (p=0.116).

Sensitivity analyses

In sensitivity analyses, we repeated all assessments using higher severity-level cut-points. We used cut-points of EPDS≥15, PHQ-9≥15, and CESD-10≥15 and did not repeat analyses for PHQ-2 since higher severity cut-points are not standard. Results from all analyses were consistent with our main findings. Prevalence patterns and kappa agreement did not appreciably change. Sensitivity decreased (40%) and specificity increased (100%) for both the CESD-10 and EPDS in ROC curve analyses at the revised cut-points. Symptomatology did not meaningfully change; the magnitude of effects of IPV and social support on postpartum depressive symptoms was higher, with wider 95% confidence intervals which encompassed original estimates of MSD symptoms. We repeated all analyses among the subset of participants with depressive symptom data in all scales (n=2328). Results for MSD prevalence, diagnostic performance, and symptomatology did not change meaningfully. Cofactor associations were no longer statistically significant, likely due to insufficient power.

Discussion

Main findings

In this comparative evaluation of four commonly used depression screening scales in a large cohort of postpartum Kenyan women, we found that the CESD-10, EPDS, PHQ-9, and PHQ-2 varied widely in detection of moderate-to-severe depressive symptoms. The CESD-10 and EPDS demonstrated high diagnostic performance to identify probable MDD. Depressive symptoms reported most frequently by women with MSD differed, indicating that scales identified women with different manifestations of depressive symptoms, potentially explaining the lack of strong agreement between scales. Our evaluation of the known epidemiologic relationships between IPV, social support, and postpartum MSD symptoms showed significant associations with moderate differences in strength of association between the scales. To our knowledge, this is the first study to compare the performance of the CESD-10, EPDS, PHQ-9, and PHQ-2 in a

large cohort of postpartum African women. Our results highlight tradeoffs for tool selection which has implications for research and practice.

Interpretation

Prevalence of MSD symptoms in early postpartum ranged from 3%-13% depending on the depression screening scale used. These estimates are consistent with prevalence estimates in similar research and clinical settings of SSA [40,70]. A recent systematic review and meta-analysis of postnatal depression in Africa revealed a pooled prevalence of 16.8% and yielded prevalence estimates similar to those in our study with specific depression screening tools: 21.4% with CESD-10 in Zimbabwe, 9.2% with EPDS in Sudan, and 7.0% with PHQ-9 in Ghana [70]. To date, most studies have estimated prevalence of MSD symptoms using a single screening scale. Our study was unique in concurrently assessing 4 tools and demonstrated up to a 2-fold difference in prevalence of depression between scales.

Our findings suggest that variability in depression prevalence observed between studies may be a result of different scales used in assessing depression [40,70]. These differences have implications for who receives more-intensive (e.g., referral to specialized psychiatric care) versus less-intensive (e.g., psychological support, self-help messages) mental health intervention within health systems. The PHQ-9 would result in the lowest number of referrals for higher-intensity services (32 per 1000 women screened), referrals with the PHQ-2 would also be low (49 per 1000 women screened), while the CESD-10 scale would produce the highest volume (126 referrals per 1000 women screened). Multi-stage screening approaches that utilize brief and longer depression screening scales, may help optimize allocation of available resources for maternal mental health in low-resource settings [99]. The WHO recommends task-shifted depression evaluation by non-specialized healthcare providers through two screening questions consistent with the PHQ-2, followed by more comprehensive questions similar to the PHQ-9 (mhGAP approach) [99]. Our results support this approach in MCH settings.

We found slight-to-moderate agreement between scales. A prior study that evaluated agreement between the EPDS and PHQ-9 depression scales among 1500 pregnant women in Peru similarly found moderate agreement (kappa=0.36). We found higher agreement between PHQ-2 and PHQ-9 than a prior study (kappa 0.17) comparing PHQ-2 and PHQ-9 in 218 American pregnant women [141]. Differences in agreement between scales illustrate the varied domains assessed by each scale, which would result in differences in *numbers* of women referred, but also in *which* women would be referred.

The CESD-10 and EPDS both demonstrated strong diagnostic performance with high sensitivity, specificity, and AUROC for MSD symptoms compared to probable MDD. Of note, the reference standard for probable MDD used in this analysis was the PHQ-9 scoring algorithm for DSM-V classification of probable MDD [146]. The PHQ-9 algorithm approach was originally developed as a rapid, self-report version of the *Primary Care Evaluation of Mental Disorders* (PRIME-MD) that could be used to efficiently classify probable MDD [146]. It has also been a reference standard in diagnostic validation studies for depression screening tools when physician-led clinical diagnostic interviews were not available [156,157]. Since the PHQ-9 and PHQ-2 screening scores are comprised of the same items used to define the MDD algorithm, we did not perform ROC analyses comparing the PHQ-9 and PHQ-2 to the MDD reference standard. Overall, the CESD-10 demonstrated high sensitivity, specificity, and AUROC (0.82), while the EPDS had lower sensitivity yet was very accurate in distinguishing non-cases (AUROC: 0.75).

All tools have been separately validated in at least one study in either African perinatal (EPDS [158], PHQ-9 [120]) or general populations (CESD-10 [159], PHQ-2 [42]). To ensure those who would benefit from more intensive psychosocial treatment are not missed due to a false negative result, high sensitivity is important. In parallel, optimal specificity is necessary to avoid misallocation of higher-intensity, specialized provider time to individuals with a false positive screening result [98]. In clinical settings which rely on task-shifted mental health screening and service provision, the ideal balance between sensitivity and specificity may be influenced by

available interventions, costs, and accessibility [160]. Accepting a loss in sensitivity to ensure high specificity may help optimize resource allocation [160].

We found significant associations between MSD symptoms and IPV using all four screening tools, consistent with the published literature [149]. The association was the strongest with EPDS (RR: 2.5) and lowest with PHQ-9 (relative risk: 1.8). We also saw differences in effect size and statistical significance for relationships between MSD symptoms and social support. Our observation of varied strength of association has implications for interpreting epidemiologic studies that assess cofactors of MSD symptoms using different screening tools. The variation in prevalence estimates for MSD symptoms across the scales contributes to differences in relationships with cofactors, thus differences in such relationships between studies should not be over-interpreted.

Strengths

Our data was collected in a large (n>3000), multisite randomized cluster trial and included multiple commonly used depressive symptom scales validated in African settings. Participants were followed overt time, establishing temporality of relationships between cofactors and depression. This is the first study to directly compare the performance of the CESD-10, EPDS, PHQ-9, and PHQ-2 in a large cohort of postpartum African women.

Limitations

The PrIMA RCT did not enroll women living with HIV based on the main aim of evaluating HIV prevention strategies, which limits generalizability of our findings in settings with high HIV prevalence. Our study did not include clinical diagnosis of MDD by a specialized clinician, instead we used provisional diagnosis of probable MDD classified by the PHQ-9 algorithm as a reference standard in diagnostic performance evaluations [146]. This method allows use of PHQ-9 items for provisional MDD classification in the absence of clinical evaluation and has been used previously to evaluate diagnostic performance of depression screening tools [156,157].

Conclusion

Depression screening tools varied in detection of moderate-to-severe depressive symptoms in early postpartum between four depression screening instruments used among perinatal populations worldwide: CESD-10, EPDS, PHQ-9, and PHQ-2. These depression tools had moderate differences in symptomatology and strength of association with intimate partner violence and social support. We also saw moderate differences in diagnostic performance between the CESD-10 and EPDS compared to PHQ-9 algorithm for MDD. All scales performed well, and the PHQ-2 emerged as the depression screening tool that would balance low referral burden to the health system, while maintaining valid estimates of known epidemiologic relationships. Additionally, the brevity of the PHQ-2 as a two-item scale has advantages for application in maternal child health clinics. These results support the WHO recommendation for multi-stage screening with PHQ-2 followed by administration of a longer depression screening scale. Overall, our findings have implications for tool selection in research and clinical practice addressing depression among pregnant and postpartum women in sub-Saharan African settings.

TABLES AND FIGURES

Table 3.1. Characteristics of PrIMA participants followed through six weeks postpartum

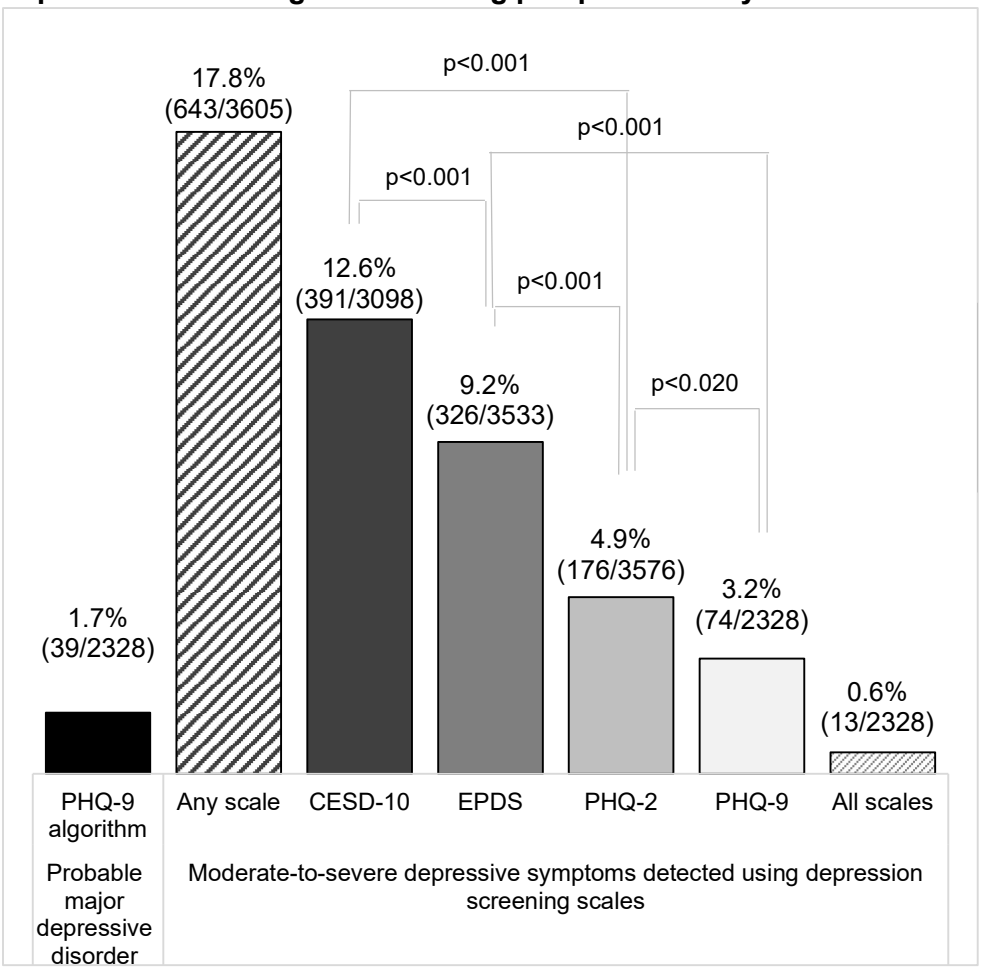
Characteristic		Overall (n=3605)	
Demographic characteristics	**N**	**N or median**	**% or IQR**
Age (years)	3603	24	21-29
Adolescents and young adults (<25 years)	3603	1991	55·3%
Married/living with a partner	3562	3069	86·2%
Currently in school	3552	284	8·0%
Completed education (years)	3524	10	8-12
Regularly employed	3552	523	14·7%
Household crowding (>3 people/room)	3567	371	10·4%
Pregnancy history			
Gestational age at enrollment (weeks)	3585	24	20-29
Ever pregnant before	3588	2750	76·6%
Number of pregnancies	3593	2	2-3
Partnership and sexual behavior characteristics			
Partner age difference >10 years*	2772	450	16·2%
Partner HIV-positive*	3318	172	5·2%
Partner HIV status unknown	3605	963	26·7%
Self-perceived HIV risk (within next year) “Extremely/very likely”	3583	1701	47·5%
Transactional sex ever in last 6 mo.	3587	59	1·6%
Forced to have sex against her will ever in last 6 mo.	3587	191	5·3%
Psychosocial characteristics			
Ever drink alcohol	3574	140	3·9%
Social support score[a]	3517	76	63-88
Low social support (MOS-SSS score <72)	3517	1262	35·9%
Intimate partner violence [b] (HITS score ≥10)	3578	368	10·3%

*Among those with a current partner

[a]We evaluated social support using the 18-item Medical Outcomes Study social support score (MOS-SSS), defining low social support as scores below 72 (Low social support: MOS-SSS score score <72 = “Yes”, MOS-SSS score ≥ 72 = “No”)

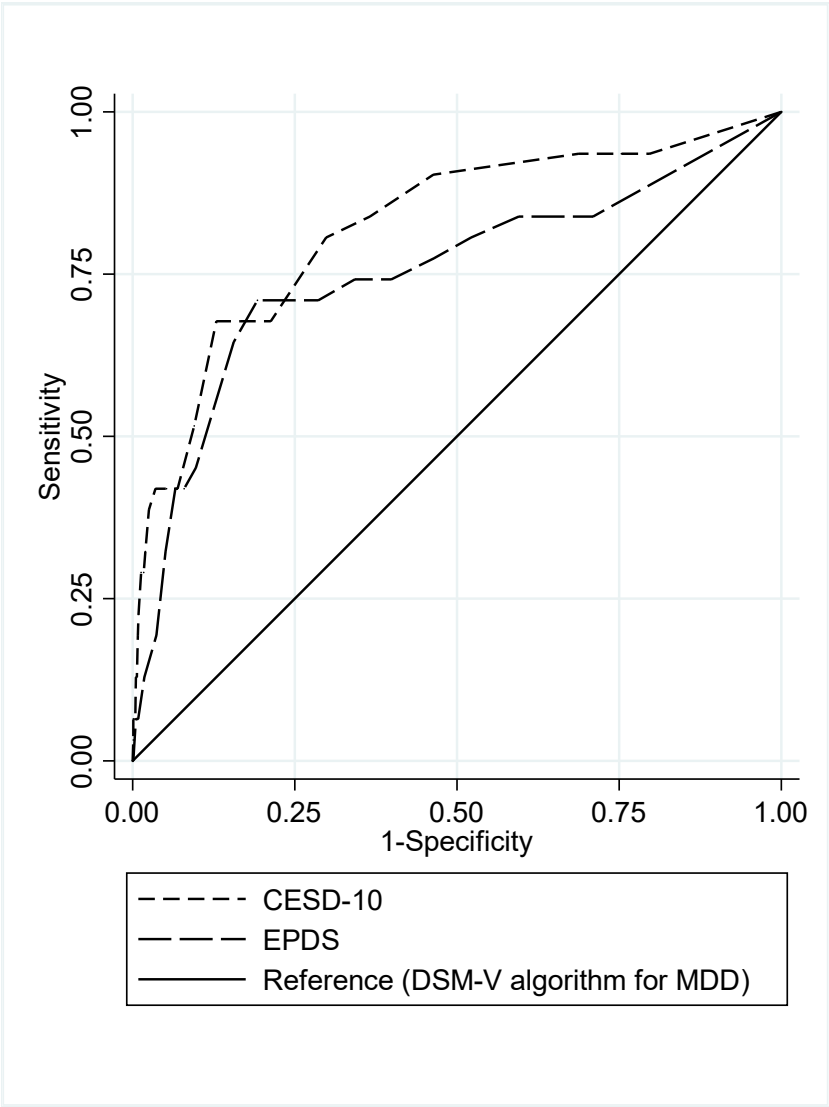
[b]We evaluated intimate partner violence using the 4-item Hurt, Insult, Threaten, and Scream scale (HITS), defining intimate partner violence as scores of 10 and above (IPV: HITS score ≥10 = “Yes”, HITS score <10 = “No”)

Figure 3.1. Comparing frequency of moderate-to-severe depressive symptoms using four depression screening scales among postpartum Kenyan women



We compared frequency of MSD between each pair of depression screening scales using McNemar's tests.
Upper and lower bound markers represent standard errors of the proportions, clustered by site.
PHQ-9 algorithm: Scoring algorithm using PHQ-9 items to define probable major depressive disorder *(Kroenke et al. 2002)*
CESD-10: Center for Epidemiologic Studies Depression Scale
EPDS: Edinburgh Postnatal Depression Scale
PHQ-9: Patient Health Questionnaire-9
PHQ-2: Patient Health Questionnaire-2
"Any scale": Proportion of participants with MSD in at least 1 scale
"All scales": Proportion of participants with MSD in all scales

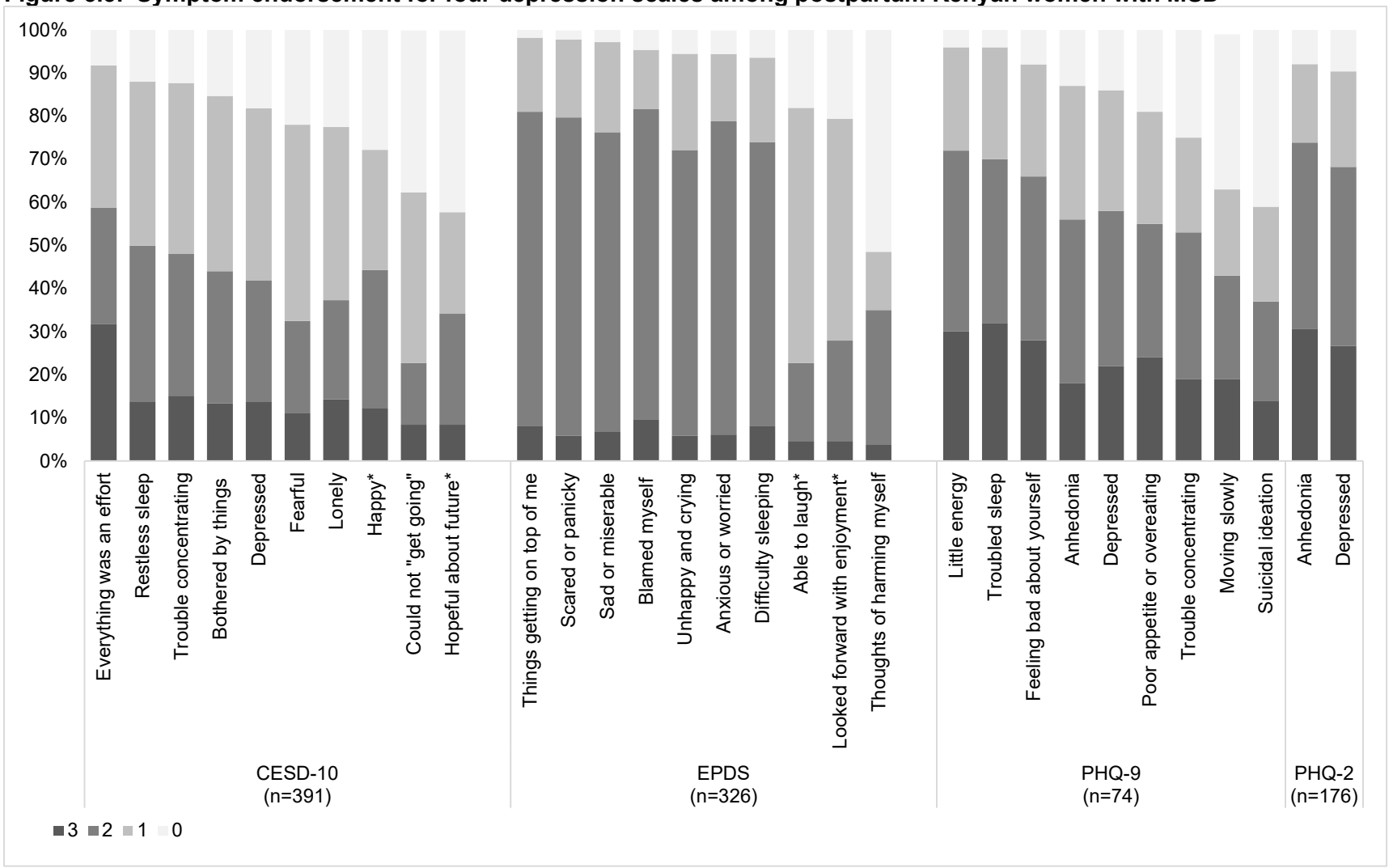
Figure 3.2. Comparing diagnostic performance of the CESD-10 and EPDS depression scales among postpartum Kenyan women (n=2328)



Depression symptom scale	Sensitivity	Specificity	AUROC
CESD-10 score ≥ 10	50·0 %	90·6 %	0·822
EPDS score ≥ 13	41·7 %	92·1 %	0·752

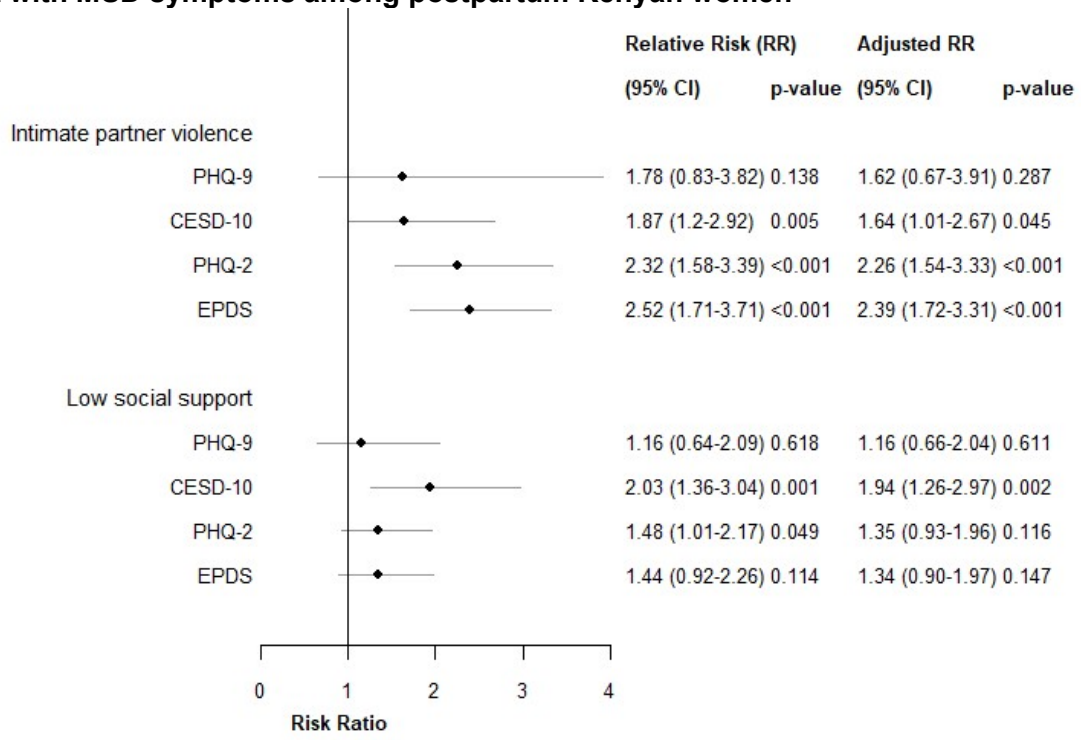
CESD-10: Center for epidemiologic studies depression scale
EPDS: Edinburgh Postnatal Depression Scale
AUROC: Area under the receiver operating characteristic curve
DSM-V algorithm for MDD: Scoring algorithm using PHQ-9 items to define major depressive disorder (MDD) *(Kroenke et al. 2002)*

Figure 3.3. Symptom endorsement for four depression scales among postpartum Kenyan women with MSD



*For most items, higher item scores denote higher frequency of a negative feeling. Items marked with * are positive feelings, where higher item scores denote lower frequency of the experience.

Figure 3.4. Epidemiologic associations between intimate partner violence and low social support with MSD symptoms among postpartum Kenyan women



Relative risks are from generalized linear regression models with binomial family and log link, clustered by facility. Multivariable models were adjusted for age (years), household crowding (>3 vs. ≤3 people/room), married/living with partner, social support score.

Chapter 4: Trajectories and predictors of perinatal depressive symptoms among Kenyan women

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Trajectories and predictors of perinatal depressive symptoms among Kenyan women: a prospective analysis from pregnancy through 9 months postpartum

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Keywords: Perinatal depression, Center for Epidemiologic Studies Depression Scale-10, , sub-Saharan Africa, mental health, pregnancy, postpartum

ABSTRACT

Background: Gaps remain in understanding longitudinal patterns and predictors of perinatal depressive symptoms in sub-Saharan Africa. This study aimed to explore trajectories of depressive symptoms and associated factors from pregnancy through 9 months postpartum among Kenyan women.

Methods: In this prospective cohort study, we analyzed data from the PrEP Implementation for Mothers in Antenatal Care study in which HIV-negative women were enrolled in pregnancy and followed through 9 months postpartum in 20 public sector maternal child health clinics in Western Kenya. Study nurses serially assessed depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CESD-10), intimate partner violence (IPV) with the Hurt, Insult, Threaten, Scream scale, and social support with the Medical Outcomes Study scale. Generalized estimating equations were used to identify correlates of moderate-to-severe depressive symptoms (MSD) (CESD-10 score ≥10) and group-based trajectory modelling (GBTM) identified patterns.

Findings: Among 3555 women, median age was 24.0 years (IQR 21.0-28.7), 1330 (38%) had low social support, and 278 (8%) reported IPV in pregnancy. All participants (3555, 100%) were female sex and all (3555, 100%) were African Kenyan ethnicity. Prevalence of MSD was higher in pregnancy than postpartum (870/3555, 24·5% vs. 597/3555, 16·8%, p<0·001). Five patterns of depressive symptoms were identified; persistent MSD in pregnancy and postpartum (295, 8%), MSD in pregnancy which resolved postpartum (139, 4%), MSD that emerged postpartum (40, 1%), chronically mild symptoms (2,709, 76%), and no depressive symptoms (372, 10%). Emergent MSD was associated with older age. Emergent, persistent, and resolving MSD were associated with pregnancy IPV; persistent MSD and resolving MSD with low social support and high HIV risk (p<0·05). MSD risk was 1·5- to 2.1-times higher with IPV, low social support, and partner HIV-positive status (p<0·05); 23% of perinatal MSD cases were attributable to low social support.

Interpretation: One third of women had perinatal MSD; 13% (474) had higher severity phenotypes of resolving, persistent and emerging MSD that may require tailored interventions. Perinatal women with comorbid psychosocial stressors such as IPV and prior pregnancy loss should be prioritized for mental health services that augment social support within routine MCH care.

Funding: National Institutes of Health

MUHTASARI

Usuli wa utafiti Bado kuna mapengo katika kuelewa aina na vibashiri vya muda mrefu vya dalili za sonona kabla na baada ya kujifungua barani Afrika kusini mwa jangwa la Sahara. Utafiti huu umelenga kuchunguza mielekeo ya dalili za sonona na sababu ambatanishi kutoka kipindi cha ujauzito hadi miezi 9 baada ya kujifungua miongoni mwa wanawake wa Kenya.

Njia Katika utafiti huu wa makundi wa muda mrefu, tulichambua data kutoka kwenye Utekelezaji wa utoaji dawa za kujikinga na maambukizi ya virusi vya ukimwi (PrEP) kwa akina Mama katika utafiti wa Utunzaji wa Ujauzito (PrIMA) ambapo wanawake wajawazito wasio na maambukizi ya virusi vya UKIMWI walifuatiliwa kwa kipindi cha hadi miezi 9 baada ya kujifungua katika kliniki 20 za afya ya mama na mtoto za umma Magharibi mwa Kenya. Wanawake wajawazito walikidhi vigezo vya kujumuishwa kwenye utafiti kama walikuwa hawajaambukizwa UKIMWI, walikuwa na umri wa miaka 15 au zaidi, walikuwa na uwezo wa kutoa ridhaa. Washiriki waliokidhi vigezo walichunguzwa na kujumuishwa kwenye utafiti kati ya Januari 15, 2018, na Julai 31, 2019, na kufuatiliwa hadi miezi 9 baada ya kujifungua, ambapo hudhurio la mwisho la utafiti wa washiriki lilifanyika Januari 15, 2021. Wauguzi watafiti walitathmini kimfululizo dalili za sonona kwa kutumia Kipimo cha Sonona cha Kituo cha Tafiti za Kiepidemiolojia (CESD-10), ukatili wa mwenzi wa karibu (IPV) chenye kipimo cha Kuumiza, Kutusi, Kutishia, Kulia, na msaada wa kijamii na kipimo cha Utafiti wa Matokeo ya Kimatibabu. Milinganyo ya ujumla ya ukadiriaji ilitumika kutambua mifanano ya dalili za wastani hadi kali za sonona (Alama ya CESD-10 ≥10) na uundaji wa mfano wa mwelekeo uliolenga makundi uligundua mielekeo tofauti ya dalili za sonona za wakati wa ujauzito na baada ya kujifungua.

Matokeo Kati ya washiriki 4447 katika utafiti mkuu wa PrIMA, 3555 walikuwa na data za dalili kamili ya sonona katika ujauzito na data za dalili ya sonona baada ya kujifungua na walihusishwa katika tathmini ya awali. Umri wa wastani ulikuwa miaka 24.0 (IQR 21.0-28.7), washiriki 1330 (38%) walikuwa na msaada mdogo wa kijamii, na 278 (8%) waliripoti ukatili wa mwenzi wa karibu katika ujauzito. Washiriki wote (100%) walikuwa jinsia ya kike na wote (100%) walikuwa Waafrika wenye asili ya Kenya. Uwepo wa dalili za wastani hadi kali za sonona ulikuwa mkubwa zaidi katika ujauzito kuliko baada ya kujifungua (870 [24·5%;95% CI 23.1-25.9] dhidi ya 597 [6·8%; 15.6-18.1]; p<0·0001). Aina tano za dalili za sonona ziligundulika; dalili za wastani hadi kali za sonona zilizo endelevu katika ujauzito na baada ya kujifungua (295 [8.3%]), dalili za wastani hadi kali za sonona zilizoisha baada ya kujifungua (139 [3.9%]), dalili za wastani hadi kali za sonona zilizotokea baada ya kujifungua (40 [1.1%]), dalili nyepesi za muda mrefu (2709 [76.2%]), na wasio na dalili za sonona (372, [10.5%]). Dalili za wastani hadi kali za sonona yaani MSD zilizojitokeza zilihusishwa na umri mkubwa zaidi. Dalili za wastani hadi kali za sonona za kujitokeza zilihusishwa na umri mkubwa zaidi. Dalili za wastani hadi kali za sonona za kujitokeza, endelevu, na zinazoisha zilihusishwa na ukatili wa mwenzi wa karibu wakati wa ujauzito; na dalili za wastani hadi kali za sonona zilizo endelevu na zinazoisha zilihusishwa na msaada mdogo wa kijamii na hatari kubwa ya UKIMWI (p zote <0·05). Hatari ya dalili za wastani hadi kali za sonona iliongezeka kwa kiwango kikubwa sana kwenye ukatili wa mwenzi wa karibu (uwiano wa uwezekano uliorekebishwa 2.07 [95% CI 1.81-2.31]; p<0.0001), msaada mdogo wa kijamii (1.74 [1.56-1.95]; p<0.0001), na hali ya mwenzi kuwa na maambukizi ya UKIMWI (1.48 [1.22-1.78]; p<0.0001). 23.34% (95% CI 18.77-27.65) ya kesi za dalili za wastani hadi kali za sonona wakati wa ujauzito hadi baada ya kujifungua zilichangiwa na msaada mdogo wa kijamii.

Tafsiri Moja ya tatu ya wanawake walikuwa na dalili za wastani hadi kali za sonona; karibu nusu ya hawa walikuwa na aina za ukubwa wa juu zaidi wa dalili za wastani hadi kali za sonona za kuisha, endelevu, na zinazojitokeza zenye ukali zaidi ambazo zinaweza kuhitaji hatua stahiki. Wanawake walio kipindi cha ujauzito hadi baada ya kujifungua wenye visababishi vya kisaikolojia na kijamii vya msongo wa mawazo kama vile ukatili wa mwenzi wa karibu na upotezaji ujauzito hapo kabla wanapaswa kupewa kipaumbele kwenye huduma za afya ya akili ambazo zitaongezea msaada wa kijamii ndani ya matunzo ya kawaida ya Afya ya Mama na Mtoto.
Ufadhili Taasisi za Taifa za Afya

Research in context

Evidence before this study

Trajectories of perinatal depressive symptoms are not well-understood globally, particularly in low- and middle-income countries (LMICs) of sub-Saharan Africa (SSA). Statistical methods to evaluate developmental trajectories over time, including latent growth curve models, growth curve mixture models, and group-based trajectory models (GBTM), have been increasingly applied to perinatal depressive symptoms over the last two decades, yet few such analyses have been conducted in LMIC populations. We searched PubMed for articles published in English published any time before February 13, 2022 using the following keywords: “depressive symptoms” OR “depression” AND “trajectories” OR “trajectory” OR “patterns” AND “pregnancy” OR “postpartum” OR “perinatal” AND all sub-Saharan African countries as defined by the World Health Organization. Our search identified only 6 analyses characterizing pregnancy and postpartum depressive symptom trajectories in LMICs in Africa (Garman et al. 2019, Garman et al. 2019, Pellowski et al. 2019, Rotheram-Fuller et al. 2018, Barthel et al. 2017, and Barthel et al. 2016), 4 in South Africa and 2 in West Africa (Ghana, Cote d’Ivoire). These studies each identified at least two distinct trajectories of depressive symptoms among African women. Studies to date have not evaluated time-varying correlates of trajectory group membership. Perinatal depressive symptom trajectories have not been evaluated in East Africa, where prevalence of perinatal depression is high, maternal child health (MCH) care is well-attended, and mental health screening and treatment could be integrated in MCH for high impact.

Added value of this study

To our knowledge, we performed the first trajectory analysis of perinatal depressive symptoms that included evaluation of time-varying correlates in a LMIC setting. It is our understanding that this is the first evaluation of perinatal depressive symptom trajectories in East Africa – a setting with increasing momentum for integrating mental health services in MCH. We found five distinct trajectories of perinatal depressive symptoms among Kenyan women; a third of perinatal women had moderate-to-severe depressive symptoms at least once during pregnancy and postpartum. Three groups had higher severity phenotypes of resolving, persisting, and emerging depression that may have distinct etiologies. Our results highlight that perinatal mental health services should augment social support, address intimate partner violence, and tailor care for women with prior pregnancy loss, as these factors influenced the timing, severity, and impact of perinatal depression.

Implications of all the available evidence

Perinatal depression is a leading cause of maternal morbidity and mortality and can influence long-term health of mothers and their children. The World Health Organization encourages expanded case identification and treatment for mental disorders through the Mental Health Gap Action Programme (mhGAP), especially in widely attended care settings like maternal and child health. However, global guidelines do not prioritize specific mental health interventions for perinatal depression or indicate who should receive these services. Our results provide new insights into phenotypes that should be prioritized for mental health care in MCH settings to optimize impact. Simultaneously screening for depressive symptoms, intimate partner violence, social support, HIV risk, and prior pregnancy loss could identify women with comorbid psychosocial stressors for higher-intensity mental health intervention. Services that improve social support, promote partner HIV testing, and address IPV may reduce or prevent perinatal depression in LMICs, especially if received during pregnancy. Our results inform next steps for implementing perinatal mental health interventions in MCH settings globally.

Introduction

Perinatal depression is the most common morbidity during pregnancy and postpartum, affecting about 10% of pregnant and breastfeeding women worldwide, with higher frequency in low- and middle-income countries (LMIC).[19] Mental health issues are among the top causes of pregnancy-related death;[161] a wide spectrum of adverse outcomes may follow perinatal depression, including maternal suicide, adverse perinatal outcomes, poor maternal-infant bonding, suboptimal infant growth, and child mental health problems.[90]

Existing studies on perinatal depression in sub-Saharan Africa (SSA) highlight high prevalence of postpartum depression (17%)[70] — even higher during pregnancy (26.3%).[162] Known cofactors of perinatal depression globally, and in SSA, include social and comorbid factors like intimate partner violence (IPV), social support, socioeconomic status, physical illness, history of mental health issues, prior adverse perinatal outcomes, and relationship factors.[19,70,84,163,164] Experiencing IPV during pregnancy is associated with 3-times higher frequency of depression.[13,70] Lacking support from partners, family, and friends is similarly related to reporting higher depressive symptoms.[19]

However, gaps remain in understanding perinatal depression in sub-Saharan Africa (SSA).[92] Most studies to date are cross-sectional, and do not characterize changes in depressive symptoms throughout the perinatal period to inform appropriate timing and groups for intervention.[165] The lack of longitudinal data limits understanding of the causal directionality of relationships with modifiable cofactors and makes it unclear whether prior or current exposures have the strongest effect on maternal mental health. Understanding the combination and timing of factors influencing experience of higher-severity perinatal depression patterns could inform appropriate intervention.

Identifying trajectories of depressive symptoms over time is increasingly used to understand patterns of perinatal depression and to define characteristics of individuals within distinct trajectories.[54,57,166] Group-based trajectory modelling is a rigorous, data-driven approach that uses maximum likelihood estimation to identify distinct groups with similar prospective

patterns of a serially measured outcome.[167] To date, no longitudinal evaluations have assessed patterns of MSD among perinatal populations in Eastern African settings. Understanding patterns and determinants of perinatal depression, could contribute insights to understanding peripartum depression and inform efficient mental health service integration and delivery within maternal child health (MCH) settings in SSA.

We aimed to serially evaluate timing, patterns, and predictors of perinatal depressive symptoms, and assess social factors over time among perinatal women attending MCH services in Kenya.

Methods

Study design and participants

This longitudinal analysis was nested in the PrEP implementation for Mothers in Antenatal Care study (PrIMA)--a cluster randomized trial conducted in Western Kenya to compare two models for pre-exposure prophylaxis implementation among pregnant women (NCT03070600).[168] Women attending antenatal care (ANC) within the 20 MCH clinics in Siaya and Homa Bay counties were screened and enrolled between January 2018 – June 2019. Pregnant women were eligible for enrollment if they were HIV-uninfected, ≥15 years old (the age of emancipation in pregnancy in Kenya), and were able to provide consent.

Procedures

Study nurses administered questionnaires in Kiswahili, Dholuo, or English languages using tablet-based REDCap surveys. We collected information about demographics, pregnancy history, partner characteristics, and psychosocial factors. To determine history of intimate partner violence (IPV), we used the 4-item Hurt, Insult, Threaten, Scream Scale with a cut-point of 10 or greater to define IPV (absolute score range: 4-20).[150] We used the 18-item Medical Outcomes Study Social Support Survey (MOS-SSS; higher scores, higher social support, range: 18-90).[151] We dichotomized this variable with a cut-point of less than 72 for low social support to enhance interpretability. We defined household crowding – a marker of socioeconomic status[155] – as the ratio of people per room in a residence greater than the median (>2 people/room). We evaluated

HIV risk using a validated risk score developed to predict HIV acquisition among perinatal women in SSA, which includes predictors of having a male partner with unknown HIV status (risk score of 6), number of lifetime sexual partners (score of 1 per partner), and recent syphilis diagnosis (within past 6 months; score of 5).[169] A HIV risk score of >6 is considered "high", corresponding to 8.9 HIV infections per 100 person-years.[169]

Outcomes

Experience of depressive symptoms was collected serially during pregnancy (enrollment visit), 6 weeks postpartum, and 9 months postpartum using the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10) where each item depicts a discrete depressive symptom. Participants rate items from 0-3 based on past-week frequency. Higher total scores denote higher severity of depressive symptoms (absolute score range: 0-30). A validated cut-point of 10 or greater denotes moderate-to-severe depressive symptoms (CESD-10 score ≥ 10; MSD).[170]

Choice of primary measure

We selected the CESD-10 to measure depressive symptoms among perinatal Kenyan women in the PrIMA study for multiple reasons. Its common application in large-scale epidemiologic studies globally improves the comparability of our findings across settings. As a 10-item scale with Likert scale response options, the burden of administration is low thus facilitating efficient screening in busy public sector MCH clinics. The CESD-10 was validated among a general population in South Africa, with acceptable-to-excellent internal consistency across three sub-populations (Cronbach's alpha: 0.69-0.89), and excellent ability to detect major depressive disorder (MDD) defined by the Mini-International Neuropsychiatric Interview (MINI) in area under the Receiver Operating Characteristic curves (AUROC) in three sub-populations (AUROC: 0.81 [95% CI: 0.71-0.90], 0.93 [95% CI: 0.90-0.96], 0.94 [95% CI: 0.89-0.99]):[159] The 20-item CESD was evaluated for validity and reliability in a Ugandan perinatal population, with high internal consistency (Cronbach's alpha: 0.92) and good detection of MDD with the MINI (AUROC: 0.82).[138] The Kenyan Ministry of Health does not currently maintain policy guidelines

specifying a perinatal depression screening scale for use in MCH settings; we will align future studies with tools specified in Kenyan policies.

Statistical analysis

Participants were included in the present analysis if they had complete depressive symptom information at the enrollment visit during pregnancy and at least one postpartum visit. The prevalence of MSD was calculated at each study visit (pregnancy, 6 weeks, 9 months postpartum). Demographic characteristics were evaluated using descriptive statistics.

We identified correlates of MSD during the perinatal period (pregnancy – 9 months postpartum) using univariable and multivariable generalized estimating equation models (GEE) with Poisson family, log link, independent correlation structure, robust standard errors, clustered by participant. In the multivariable model, we included variables hypothesized à priori to be associated with perinatal depression according to our conceptual model (Appendix) or if they were associated with perinatal MSD (alpha ≤0·1) in univariable analysis. The confounding variables included in multivariable GEE models were: age (years), not married/living with a partner (yes/no), completed education (years), household crowding (yes/no), multiparous (yes/no), prior pregnancy loss (yes/no), lifetime sexual partners >2 (yes/no), partner living with HIV (yes/no), partner HIV status unknown (yes/no), transactional sex (yes/no), forced sex (yes/no), sexually transmitted infection (yes/no), ever drinks alcohol (time-varying [current visit]; yes/no), low social support (time-varying [current visit]; yes/no), IPV (time-varying [current visit]; yes/no), pregnancy vs. postpartum (yes/no), and facility. . We estimated population attributable risk percentages (PAR%) for each correlate of perinatal MSD.

We identified discrete trajectories of perinatal depressive symptoms using GBTM – a method that groups individuals with similar patterns of an outcome measured over time using maximum likelihood estimation,[54] which has been used to identify trajectories of depression.[57,166] As a data-driven approach, researchers do not form the distinct groups themselves, but instead use model fitting to identify latent clusters. Depressive symptoms were modelled using the

continuous CESD-10 score (censored normal distribution) and time as days since enrollment. We fit the GBTM using the two-step process outlined by Nagin et al.[54] We hypothesized depressive symptoms would follow two to five distinct and clinically meaningful trajectories.[54] Thus, we fit a set of four models, each with a different number of trajectories (2-5) and used the Bayesian Information Criterion (BIC) values to identify the best-fitting model with the optimal number of trajectory groups (Appendix).[54] During this step, we modeled all trajectory groups with cubic polynomial terms, such that differences in BIC values only described fit differences due to varying the number of trajectories. Next, we fixed the number of trajectories (identified in the prior step) and ran models that differed in polynomial form of each trajectory group (e.g., linear, quadratic, cubic). We ran a separate model for each potential combination of polynomial forms, identifying the model with the optimal combination of trajectory group functional forms using BIC values.[54]

We assessed adequacy of the final GBTM through methods described by Nagin et al.[167] Group-based trajectory models calculate every individual's likelihood of belonging to each trajectory group, summarized as the "posterior probabilities of group membership". If the proportion of women belonging to each trajectory group was not meaningfully different (<5%) from the sum of individual posterior probabilities of group membership, we deemed the model was adequate. Further, we determined if the average posterior probability of membership in each group among the individuals assigned to that group was at least 70%.[54]

Nonrandom attrition in the study population over time is accommodated by a GBTM-extension method, which allows attrition to differ by trajectory group, thus relaxing the assumption of missingness at random.[54,171] Among participants with a CESD-10 score in pregnancy and at least 1 postpartum score, 78% (2783/3555) had a CESD-10 score at the 6 week visit, 90% had a CESD-10 score at the 9 month postpartum visit (3205/3555), and 69% (2438/3555) had scores for all three visits.

To illuminate each group's member profile, we assessed descriptive statistics for characteristics we identified as correlates of perinatal MSD. We evaluated these factors as

baseline predictors of depressive symptom group membership by fitting a multivariable multinomial logistic regression model. Analyses were conducted using Stata 15.

Ethical considerations

The study protocol, informed consent forms, and data collection tools were approved by the Kenyatta National Hospital-University of Nairobi Ethics Research Committee and University of Washington Human Subjects Review Committee. All participants provided written informed consent.

Role of funding sources

Funding agencies had no role in writing this manuscript or submitting for publication.

Results

Among PrIMA study participants, 97% (4299/4447) attended at least 1 postpartum visit when depressive symptom information was collected, of which 91% (3882/4257) had complete depressive symptom data in pregnancy; 92% of those (3555/3882) also had depressive symptom data in postpartum and were included in this analysis. All participants (n=3555, 100%) were female sex and all (n=3555, 100%) were African Kenyan ethnicity. Participants contributed a median of 379 person-days of follow-up time (Interquartile range [IQR]: 334-430, total 1,330,257 person-days). The median age was 24.0 (interquartile range [IQR]: 21.0-28.7), the majority (3021, 86%) were married, and most had previously experienced pregnancy (2693, 76%) (Table 1). Women had a median education of 10 years (IQR: 8-12); only 14% (491) of women were formally employed. About half (1725, 49%) of women experienced household crowding (>2 people/room). Over 1 in 3 women (1330, 38%) experienced low social support during pregnancy (median social support score:75 [IQR: 62-88]). About 35% (1257) of women were deemed high risk for HIV acquisition. Intimate partner violence was reported by 8% (278) of women during pregnancy. We did not detect differences in social support, IPV, HIV risk, or frequency of MSD during pregnancy between those included in the analysis because they had depressive symptom data in pregnancy and postpartum versus those not included (pregnancy scores only) (Appendix).

One in four women (24·5%, 870/3555, 95% CI:23·1-25·9) had MSD at enrollment during pregnancy (median gestational age: 25 weeks, IQR: 20-30) (Appendix). Prevalence of MSD was lower during postpartum (16·8%, 597/3555; 95% CI:15·6-18·1; p-value<0·001 from McNemar's test of pregnancy vs. postpartum), and declined from 6 weeks (12·2%, 340/2783, 95% CI: 11·0-13·5) to 9 months postpartum (10·5%; 336/3210, 95% CI: 9·4-11·6; p-value: 0·033 from McNemar's test for 6 weeks vs. 9 months postpartum). Overall, 8·7% (308/3555, 95% CI: 7·8-9·6) of women had MSD only in postpartum and 33·1% (1178/3555, 95% CI: 31·6-34·7) of women experienced MSD at some point during the perinatal period. Frequency of MSD during pregnancy varied significantly by facility (range: 6/150, 4.0% - 119/179, 66.0%, p<0.001) (Appendix).

Women who were not married or living with a partner had over 50% higher frequency of MSD compared to married women (adjusted Relative Risk [aRR]: 1·6, 95% CI: 1·3-1·8) (Table 4.2, Figure 4.1). Frequency of MSD was twice as high among those reporting IPV (aRR: 2·1, 95% CI: 1·8-2·4). Having low social support was associated with nearly twice the frequency of perinatal MSD (aRR: 1·7, 95% CI: 1·6-2.0). Associations for both IPV and social support with MSD were stronger with current than prior experiences. Women with a partner living with HIV (aRR: 1·5, 95% CI: 1·2-1·8), a partner with unknown HIV status (aRR: 1·2, 95% CI: 1·1-1·4), and those with over 2 lifetime sexual partners (aRR: 1·2, 95% CI: 1·1-1·4) had about 20% higher frequency of MSD compared to those without these factors. Women who were forced to have sex against their will had 50% higher frequency of MSD compared to those without this experience (aRR: 1.5, 95% CI: 1.2-1.7). Recent sexually transmitted infection (STI) within 6 months of enrollment was associated with 30% higher MSD prevalence than those not reporting recent STI (aRR: 1.3, 95% CI: 1.0-1.7). Frequency of MSD during pregnancy was higher than postpartum MSD (aRR: 2·1, 95% CI: 1·9-2·3).

Age, household crowding, prior pregnancy loss, alcohol use, and transactional sex were not associated with MSD after adjusting for confounders in multivariable analyses (Table 4.2, Figure 4.1). In sensitivity analyses, we evaluated correlates of MSD during pregnancy separately from postpartum. Low social support, IPV, and lifetime number of sexual partners were associated

with MSD in both periods with other cofactors associated with only pregnancy or only postpartum MSD (Appendix).

Based on population attributable risk proportions, over one in five (23·3%, 95% CI: 18·8-27·7) (Table 4.2) perinatal MSD cases were attributable to low social support. The next highest proportion of perinatal MSD cases was attributable to having more than 2 lifetime sexual partners (14·1%, 95% CI: 1·0-25·5). IPV accounted for 8% of perinatal MSD cases (7·6%, 95% CI: 5·8-9·3), while experiencing household crowding accounted for 7% of perinatal MSD cases (6.8%, 95% CI: 1.7-11.7), and being unmarried accounted for about 6% of MSD cases (5·6%, 95% CI: 3·3-7·8). Nearly 7% of the perinatal MSD cases were attributable to having a partner with unknown HIV status (6·8%, 95% CI: 2·9-10·6). About 2% of perinatal MSD cases were attributable to having a partner living with HIV (1.7%, 95% CI: 0.8-2.6), and 1% were attributable to having a recent STI (1.1%, 95% CI: 0.01-2.1).

Five discrete depressive symptom groups were illuminated by group-based trajectory modelling (Figure 4.2). Women with MSD persisting from pregnancy into postpartum clustered within one depressive symptom group (“Persistent MSD”, 295/3555, 8·3%) with a cubic polynomial form. In another group, women had MSD that emerged in postpartum following mild depressive symptoms during pregnancy (“Emergent MSD”, 40/3555, 1·1%, cubic). About 4% of women had MSD in pregnancy which resolved to mild depressive symptoms postpartum (“Resolving MSD”, 139/3555, 3·9%, quadratic). The majority of women had chronically mild depressive symptoms throughout the perinatal period (“Chronic mild”, 2709/3555, 76·2%, quartic). The model fitting process using maximum likelihood estimation grouped women into this category for their similarity in average “mild” depressive symptom scores over time. Some of the women included in this group experienced one episode of MSD with a CESD-10 score just above 10 during the perinatal period (Appendix). About one in ten women never had depressive symptoms from pregnancy through 9 months postpartum (“No depressive symptoms”, 372/3555, 10·5%, linear).

This was the best fitting model (BIC = -26648.8, AIC = -26525.5, Log Likelihood =-26485.5) and model adequacy was supported (Appendix). The average posterior probability of being allocated to a depressive symptom group among women assigned to that group was >70% for all groups (absolute range: 71·9%-90·8%). The proportion of women in each depressive symptom group was well-aligned (≤5%) with the proportion expected in each group based on the sum of posterior probabilities.

We further evaluated the time-varying influence of IPV and low social support on depressive symptom patterns by including them as predictors in the GBTM model. The adjusted patterns were uniform in shape over time, stratified by severity level, implying the contributions of these factors to the dynamic shapes differentiating depressive symptom groups (Figure 4.3).

Generally, members of the “Persistent MSD” or “Resolving MSD” group had the highest effect sizes for predictors followed by the “Emergent MSD” group, when compared to the “no depressive symptoms” group (Figure 4.4, Appendix). Membership in the “Persistent MSD” and “Resolving MSD” groups was associated with IPV, low social support, and high HIV risk (effect sizes range: 1·7-6·2). Prior pregnancy loss was also associated with being in the “Persistent MSD” group (adjusted Odds Ratio [aOR]: 1.9, 95% CI: 1.2-3.1). The strongest predictor of “Resolving MSD” was IPV experienced during pregnancy (aOR: 6·2, 95% CI: 31-12·3), whereas the strongest predictor of “Persistent MSD” was low social support (aOR: 5·3, 95% CI: 3·8-7·5). Older age (>24 years old) was associated with membership in the Emergent MSD group (aOR: 2·2, 95% CI: 1·1-4·4), as was IPV (aOR: 4.0, 95% CI: 1.4-11.4).

Within the “Persistent MSD” group, the majority (65%, 190/295) of women reported low social support during pregnancy which remained through 9 months postpartum—the highest across all groups (Appendix). Over half experienced high HIV risk (48%, 141/295) and household crowding (53%, 156/295). One in six of “Persistent” group members reported IPV during pregnancy (17%, 51/295)—the second highest proportion across groups, and IPV prevalence decreased over time. Median CESD-10 scores were relatively consistent across visits.

Members of the “Emergent MSD” depressive symptom group had a high frequency of reported IPV (15%, 6/40) during pregnancy, which increased slightly by the 9-month postpartum visit (18%, 7/40). About 15% (6/40) of “Emergent MSD” members had a prior pregnancy loss, which was the second highest frequency across all groups. Median CESD-10 scores were severe at the 9-month visit (22, IQR: 20-27).

The “Resolving MSD” group had the largest proportion of women with high HIV risk (49%, 68/139) and the largest proportion of unmarried women (27, 20%). Over 1 in 5 women reported IPV during pregnancy (25%, 34/139), which was also the highest frequency across groups. Prevalence of IPV was lower at 9 months postpartum (4%, 5/139). This group reported low social support consistently across visits. Median CESD-10 scores were severe during pregnancy (19, IQR: 17-22), mild thereafter. The “Chronic mild” and “No depressive symptoms” groups had similar characteristics.

Discussion

In this large prospective analysis among perinatal Kenyan women followed from pregnancy through 9 months postpartum in public sector MCH care, we found high prevalence (33%) of MSD at least once during the perinatal period, with higher frequency in pregnancy than postpartum. To our knowledge, this is the largest study to evaluate perinatal depressive symptom trajectories among women in a LMIC setting-- the first in Eastern Africa, to our knowledge.

Five distinct trajectories described phenotypes of depressive symptom experiences over time. About 13% of women had a higher severity depressive symptom pattern with MSD that either persisted throughout the perinatal period, resolved after pregnancy, or emerged postpartum. Most women had mild depressive symptoms throughout the perinatal period; some with episodic symptom scores just above the threshold for MSD. IPV, low social support, or being at high risk for HIV were cofactors of perinatal MSD and predicted membership in higher severity depressive symptom groups.

Our estimate of MSD during pregnancy (25%) aligned with the pooled prevalence from a recent meta-analysis among African women (26%),[162] as did our estimate of postpartum

depression prevalence (17%).[70] Associations of perinatal MSD with IPV, low social support, and being unmarried are consistent with results from SSA[70] and other LMICs.[19] Few studies have assessed associations between HIV risk factors and depression among pregnant and breastfeeding women. Our findings echo associations between HIV risk behaviors and mental health outcomes among non-pregnant women at high HIV risk.[172] Women with HIV risk factors in our study had higher frequency of perinatal depression, highlighting potentially synergistic benefits of integrating HIV prevention and mental health services within MCH settings.

To understand the impact of each cofactor on perinatal depression, we estimated population attributable risk proportions, which considers effect size and prevalence of the factor. Low social support accounted for >20% of perinatal depression cases, because low social support was common (50%) and doubled one's risk for depression. About 7% of perinatal depression cases could be potentially avoided if all women were aware of their partners' HIV status; another 7% if IPV was prevented. Our findings suggest that integrated efforts to enhance social support, increase partner HIV testing and eliminate IPV could decrease peripartum depression by 34%.[173] Population attributable risk proportion should be considered in conjunction with feasibility. modifiability, and cost-effectiveness when selecting interventions to impact perinatal depression in resource-limited settings.

In GBTM analysis, 8% of women had persistent depression, similar to estimates from prior perinatal depressive GBTM analyses in South Africa (3·1%-8·6%).[59,174–176] Women in this group had comorbid stressors of high HIV risk, prior pregnancy loss, and IPV, as well as the highest proportion of low social support through 9 months postpartum. Low social support in the context of multiple coexisting life stressors may perpetuate depressive symptoms in this group. About 4% of perinatal women had severe depressive scores during pregnancy with symptoms decreasing to mild or low levels after delivery, similar to a prior study (1·3%).[176] This group had the highest frequency of IPV, high HIV risk, household crowding and the greatest proportion of unmarried women. Depressive symptoms for some women in this group may have resolved because HIV risk did not result in HIV acquisition or when IPV resolved postpartum. A small group (1·1%) had

mild or low depressive symptoms during pregnancy that increased to MSD postpartum, similar to prior studies (2·2%-10·1%).[174–176] Defining characteristics of this group included older age and high frequency of prior pregnancy loss. Unlike other groups, women in this group reported IPV more frequently 9 months postpartum, perhaps precipitating postpartum depressive symptoms. Median depressive symptom scores in this group reached the highest severity of any group. Our GBTM findings suggest that perinatal women with comorbid stressors should be prioritized for mental health services, particularly those reporting IPV, since IPV had the strongest influence on dynamic changes in depressive symptoms. Interventions that increase social support may interrupt persistent perinatal depression. Older women, especially those with prior pregnancy loss, should be monitored for emergent postpartum depression.

We identified a large group (76%) with chronic mild depressive symptoms throughout the perinatal period, as did similar studies in SSA (71·1%-91·5%).[174–176] While median CESD-10 scores in this group were mild over time, some members had episodes of MSD with scores just above the referral threshold (referral score ≥10). They represented the remaining 20% of women ever reporting MSD besides the 13% with higher severity patterns. Based on these results, over half of perinatal MSD cases identified by CESD-10 screening may occur among women with a less concerning pattern of depressive symptoms. The higher severity groups identified in our study may offer a more accurate estimate of perinatal depression.[177] The chronic mild group may be sufficiently supported by lower-intensity psychosocial services, whereas women with higher severity symptoms could be prioritized for mental health services with higher provider time and resource allocation. Cognitive behavioral therapy, interpersonal therapy, and problem-solving counseling have been shown to be effectively delivered by lay counselors in low-resource settings[178] and could be integrated into MCH care in SSA, where high attendance to antenatal care and postnatal care is high (>90).

Our data were collected serially in a large, multisite randomized cluster trial. This enabled a trajectory analysis to better understand changes in maternal mental health over time using GBTM--a rigorous, data-driven method. We estimated PAR% to expand existing evidence about

cofactors of perinatal depression on population-level impact. The PrIMA study did not enroll women living with HIV, which could limit generalizability of our findings in settings with high HIV prevalence. Our study did not include clinical diagnosis of depression by a clinician, thus we may have misclassified this outcome. We used a validated screening scale to classify MSD, which has been used in multiple studies in sub-Saharan Africa.[138,159] We used GBTM extension methods to account for potential non-random attrition in this pragmatic trial.[171] We acknowledge that we were unable to account for the contributions of unmeasured factors on changes in depressive symptoms over time, such as changing perceptions or attitudes about pregnancy outcomes, comorbid physical health conditions, and other mental health conditions (e.g., stress, anxiety). The present analysis does not evaluate PrEP use behavior (the main outcome of the parent study) as a potential correlate of MSD. Other analyses from our team specifically assess relationships between psychosocial factors and prospective PrEP use among perinatal Kenyan women.

A third of perinatal Kenyan women attending public sector MCH services had moderate-to-severe depressive symptoms at some point during the perinatal period, with higher prevalence in pregnancy compared to postpartum. A subset of women had severe MSD that persisted from pregnancy to postpartum, resolved during the postpartum period, or emerged postpartum. These groups could particularly benefit from mental health intervention. Women with mild depressive symptoms close to the screening threshold could be offered lower-intensity psychosocial support. Experience of IPV, lower social support, being unmarried, and having a partner known to be living with HIV or of unknown HIV status predicted perinatal MSD. Low social support accounted for the highest proportion of depression cases and was associated with higher severity patterns. Interventions addressing depressive symptoms which enhance social support and increase partner HIV testing should be integrated into MCH services and prioritized for those reporting IPV and prior pregnancy loss.

Declaration of interests:

This paper represents the opinions of the authors and is not meant to represent the position or opinions of organizations, nor the official position of any staff members. Ms. Larsen reports grants from NIH during the conduct of the study. Dr. John-Stewart reports grants from NIH, grants from CDC, grants from Thrasher, personal fees from UpToDate, personal fees from UW, grants from IMPAACT, outside the submitted work. Dr. Kinuthia reports grants from NIH, during the conduct of the study. Dr. Pintye reports grants from NIH during the conduct of the study.

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Authorship:

AL-conceptualized the idea for the article, had access to raw data, performed and verified data analyses, wrote the first draft, conducted the edits for the drafts, drafted the figures and tables, reviewed and approved final draft, and made the decision to submit for publication.

JP-reviewed the data in the figures and tables, had access to raw data, reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft.

MM- performed data management, had access to raw data, accessed and verified the data, reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft.

SW- performed data management, had access to raw data, reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft.

JK- directed study operations, reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft.

FA- managed study operations and study team, had access to raw data, reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft.

BR-oversaw statistical analysis, reviewed drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft.

LG- reviewed drafts and provided substantial edits and contributed towards final draft, had access to raw data, reviewed and approved final draft.

JD- reviewed drafts and provided substantial edits and contributed towards final draft, had access to raw data, reviewed and approved final draft.

GJS- conceptualized the idea for the article, reviewed the data in the figures and tables, reviewed all drafts and provided substantial edits and contributed towards final draft, reviewed and approved final draft, and made the decision to submit for publication.

Data sharing statement: Upon publication, de-identified participant data that underlie the results will be available upon request to the corresponding author.

TABLES AND FIGURES

Table 4.1. Baseline characteristics of PrIMA study participants included in depression analyses (n=3555)

Demographic characteristics	n	n or median	% or IQR
Age (years)	3553	24·0	21·0-28·7
Older adults (>24 years)	3553	1552	43·7
Gestational age (enrollment)	3555	24·0	20·0-29·4
Not married or not living with a partner	3522	501	14·2
Completed education (years)	3488	10·0	8·0-12·0
Regularly employed	3515	491	14·0
Household crowding (≥2 people/room)	3529	1725	48·9
Pregnancy history			
Multigravida	3551	2693	75·8
Prior pregnancy loss	3544	447	12·6
Prior preterm birth	3555	29	0·8%
Partnership and sexual behavior characteristics			
Lifetime sexual partners	3549	2·0	2·0-3·0
Lifetime sexual partners (>2)	3549	2957	83·3
Partner age difference >10 years (among those with a partner)	2734	428	15·7
Partner living with HIV	3507	144	4·1
Partner HIV status unknown	3507	1054	30·1
High HIV risk[1]	3555	1257	35·4
Transactional sex ever (last 6 mo.)	3549	57	1·6
Forced to have sex against her will (last 6 mo.)	3550	199	5·6
Sexually transmitted infection (enrollment)	3550	91	2·6
Psychosocial characteristics			
Ever drink alcohol	3539	141	4·0
Social support score[2]	3489	75·0	62·0-88·0
Low social support[2] (MOS-SSS score <72)	3489	1330	38·1
Intimate partner violence[3] (HITS score ≥10)	3550	278	7·8

[1]We evaluated HIV risk using the Pintye et al.[169] risk score (high HIV risk: score >6 = "Yes", score ≤6 = "No").
[2]We evaluated social support using the 18-item Medical Outcomes Study social support score (MOS-SSS), defining low social support as scores below 72 (Low social support: MOS-SSS score score <72 = "Yes", MOS-SSS score ≥ 72 = "No").
[3]We evaluated intimate partner violence using the 4-item Hurt, Insult, Threaten, and Scream scale (HITS), defining intimate partner violence as scores of 10 and above (IPV: HITS score ≥10 = "Yes", HITS score <10 = "No").

Table 4.2. Longitudinal correlates of perinatal moderate-to-severe depressive symptoms from pregnancy through 9 months postpartum (n=3555)

	Univariable Analysis Moderate-to-severe depressive symptoms (MSD)[d] vs. No MSD			Multivariable Analysis MSD vs. No MSD[1]			Population attributable risk % (PAR%)[2]	
	RR	95% CI	p-value	aRR	95% CI	p-value	PAR%	95% CI
Baseline factors								
Demographic characteristics								
Age (years)	1·01	1·00-1·02	0·046	1·00	0·99-1·01	0·950		
Older age (>24 years)	1·07	0·97-1·19	0·179					
Not married or not living with a partner	1·14	0·99-1·31	0·068	**1·55**	**1·31-1·82**	**<0·001**	5·58	3·34-7·78
Completed education (years)	1.00	0·98-1·01	0·612	1.00	0·98-1·01	0·808		
Regularly employed	0·92	0·78-1·07	0·270					
Household crowding (>2 people/room)	1·17	1·05-1·30	0·003	1·15	1.04-1.27	0·008	6.79	1.65-11.67
Pregnancy characteristics								
Multigravida	1·20	1·05-1·36	0·006	1·08	0·92-1·26	0·346		
Prior pregnancy loss	1·25	1·08-1·44	0·003	1·06	0·93-1·22	0·356		
Prior preterm birth	0.99	0·52-1·95	0·979					
Partnership and sexual behavior characteristics								
Lifetime sexual partners > 2	1·36	1·15-1·60	<0·001	**1·19**	**1·01-1·40**	**0·034**	14·12	1·03-25·48
Partner age difference >10 years	1·04	0·89-1·23	0·605					
Partner living with HIV	1·20	0·97-1·50	0·096	**1·48**	**1·22-1·78**	**<0·001**	1·68	0·75-2·60
Partner HIV status unknown	1·47	1·33-1·64	<0·001	**1·23**	**1·09-1·38**	**0·001**	6·80	2·86-10·58
High HIV risk[a]	1·48	1·34-1·64	<0·001					
Transactional sex (last 6 mo.)	1·53	1·11-2·13	0·010	1·01	0·70-1·45	0·953		
Forced to have sex (last 6 mo)	1·53	1·28-1·84	<0·001	1·47	1·24-1·74	<0·001	2.65	1.32-3.96
Sexually transmitted infection (last 6 mo)	1·72	1·37-2·15	<0·001	1·32	1.03-1.70	0·028	1.18	0.01-2.13
Psychosocial factors (baseline)								
Ever drinks alcohol	1·46	1·17-1·82	0·001					
Low social support [b]	1·82	1·64-2·01	<0·001					
Intimate partner violence [c]	2·00	1·76-2·28	<0·001					
Psychosocial factors (time-varying; currently)								
Ever drinks alcohol	1·63	1·29-2·04	<0·001	1·06	0·84-1·35	0·621		
Low social support [b]	2·40	2·18-2·64	<0·001	**1·74**	**1·56-1·95**	**<0·001**	23.34	18.77-27.65
Intimate partner violence [c]	2·83	2·52-3·18	<0·001	**2·07**	**1·81-2·36**	**<0·001**	7.57	5.83-9.27
Pregnancy vs. postpartum	2·17	2.00-2·36	<0·001	**2·07**	**1·85-2·31**	**<0·001**		

[1]Adjusted relative risks are additionally adjusted for the variables depicted here, as well as facility, since moderate-to-severe depressive symptoms varied significantly by facility (Appendix). [2]Population attributable risk % were calculated for all factors significant at p-value<0.05 in multivariable analysis, except for pregnancy status since the number of study visits taking place during pregnancy versus postpartum influenced the PAR%.

[a]We evaluated HIV risk using the Pintye et al.[169] risk score (high HIV risk: score >6 = "Yes", score ≤6 = "No").

[b]We evaluated social support using the 18-item Medical Outcomes Study social support score (MOS-SSS), defining low social support as scores below 72 (Low social support: MOS-SSS score <72 = "Yes", MOS-SSS score ≥ 72 = "No").

[c]We evaluated intimate partner violence using the 4-item Hurt, Insult, Threaten, and Scream scale (HITS), defining intimate partner violence as scores of 10 and above (IPV: HITS score ≥10 = "Yes", HITS score <10 = "No").

[d]We evaluated moderate-to-severe depressive symptoms using the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10), defining MSD as scores of 10 and above (MSD: CESD-10 score ≥10 = “Yes”, CESD-10 score <10 = “No”).

Figure 4.1. Correlates of ever perinatal MSD and population attributable risk percentages

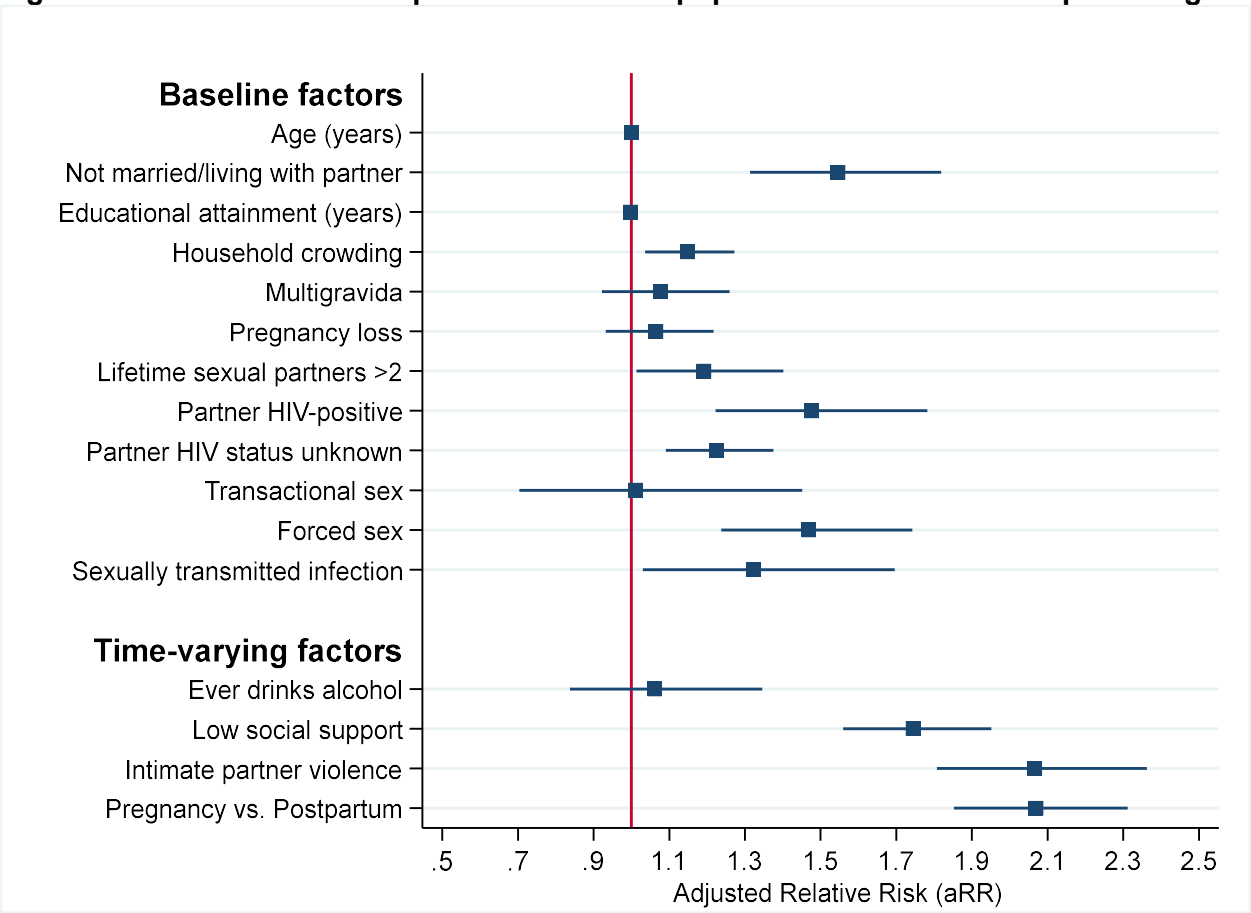
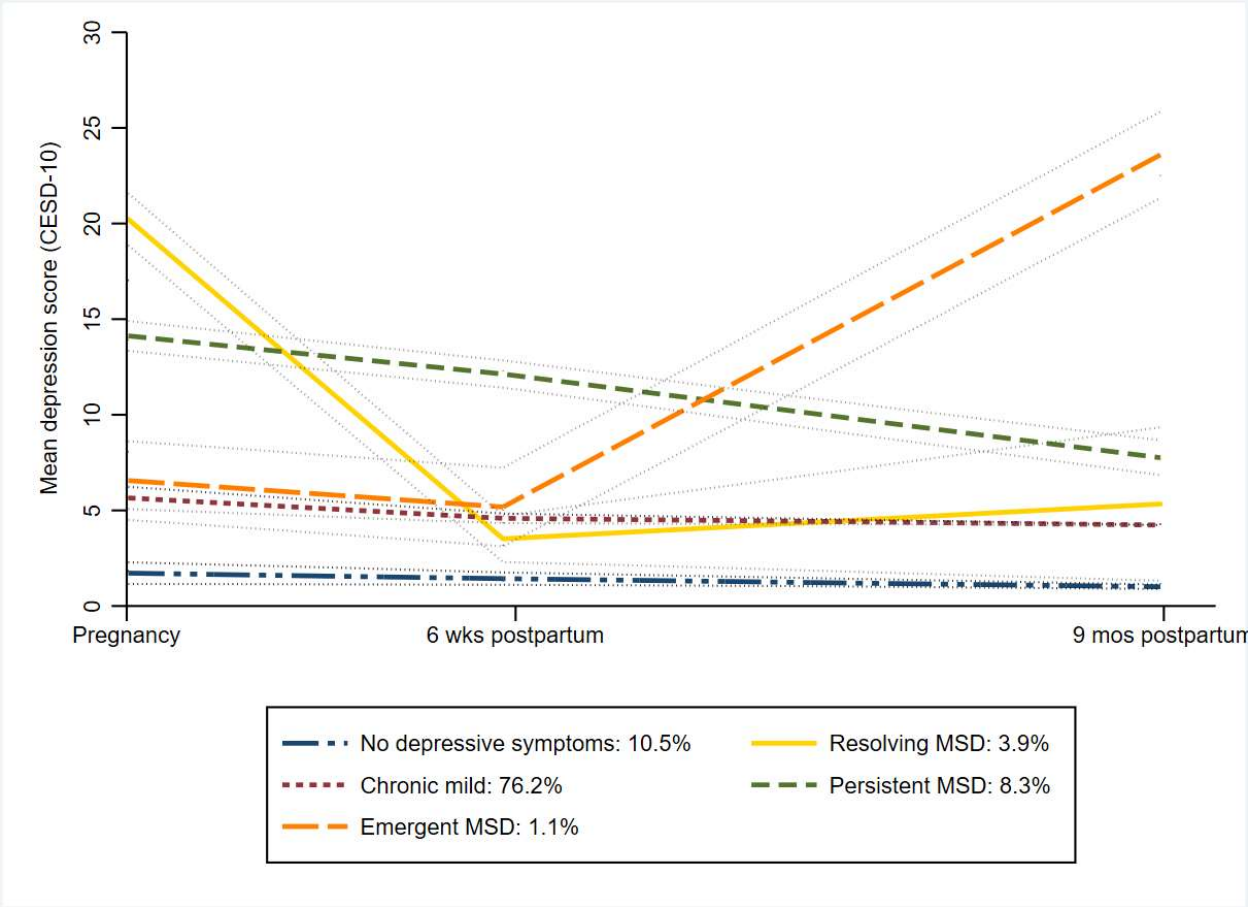
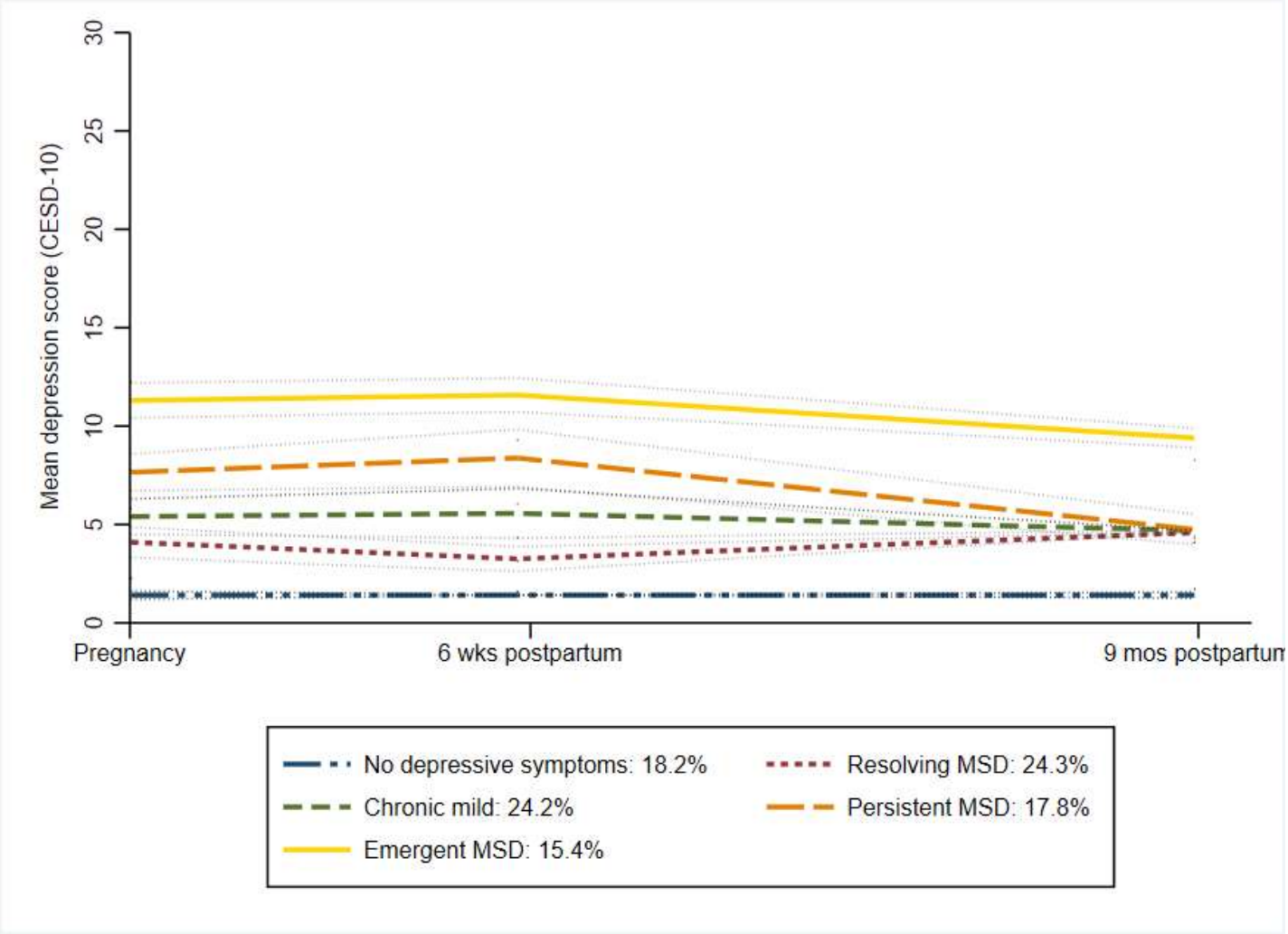


Figure 4.2. Trajectories of depressive symptoms from group-based trajectory model (n=3555)



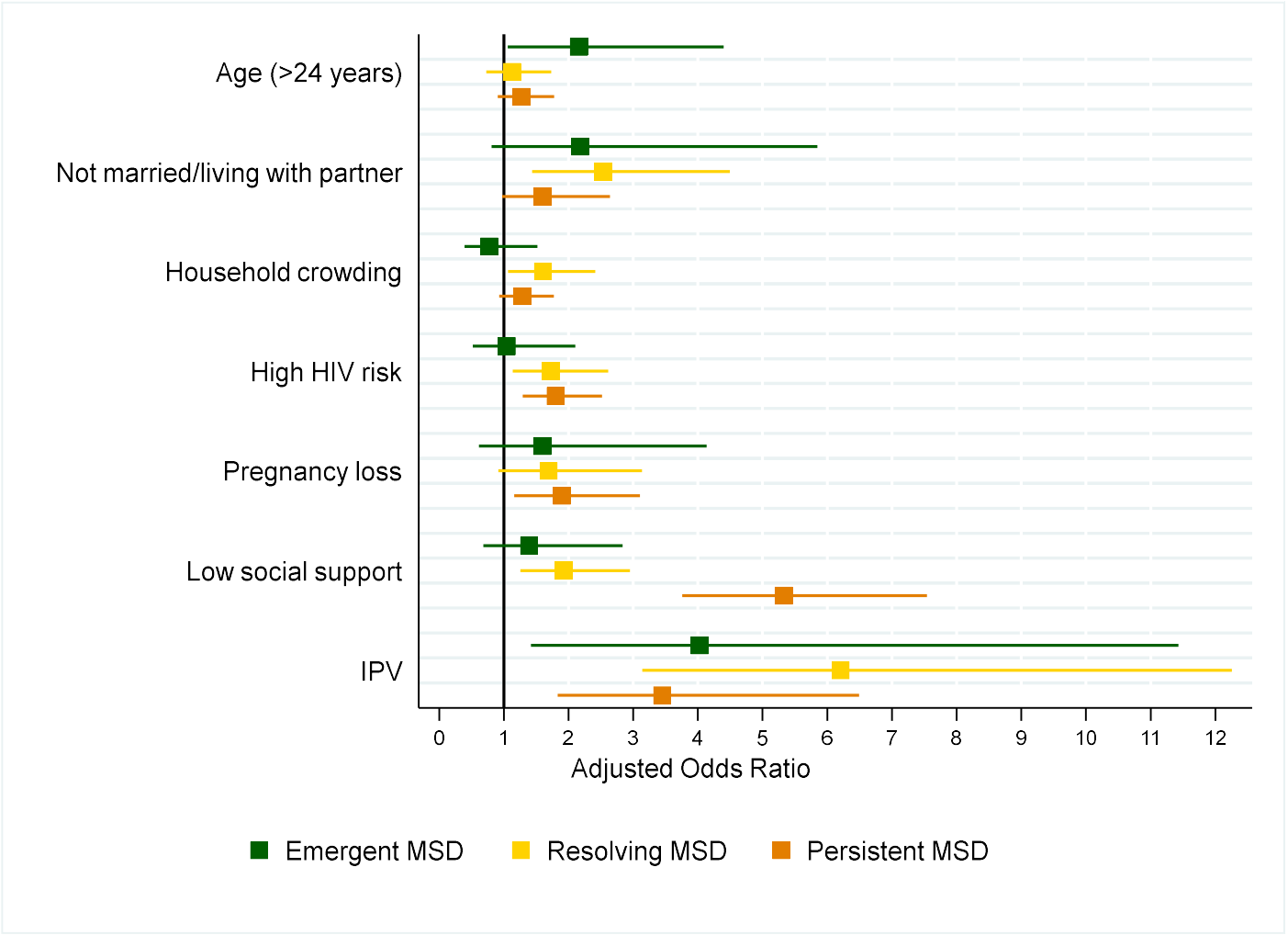
Group-based trajectory model was fit using Center for Epidemiologic Studies Depression Scale (CESD-10) as a continuous score (range 0-30), modelled as censored normal distribution, over time since enrollment (days).

Figure 4.3. Trajectories of moderate-to-severe depressive symptoms from group-based trajectory model, adjusted for time-varying intimate partner violence and low social support (n=3555)



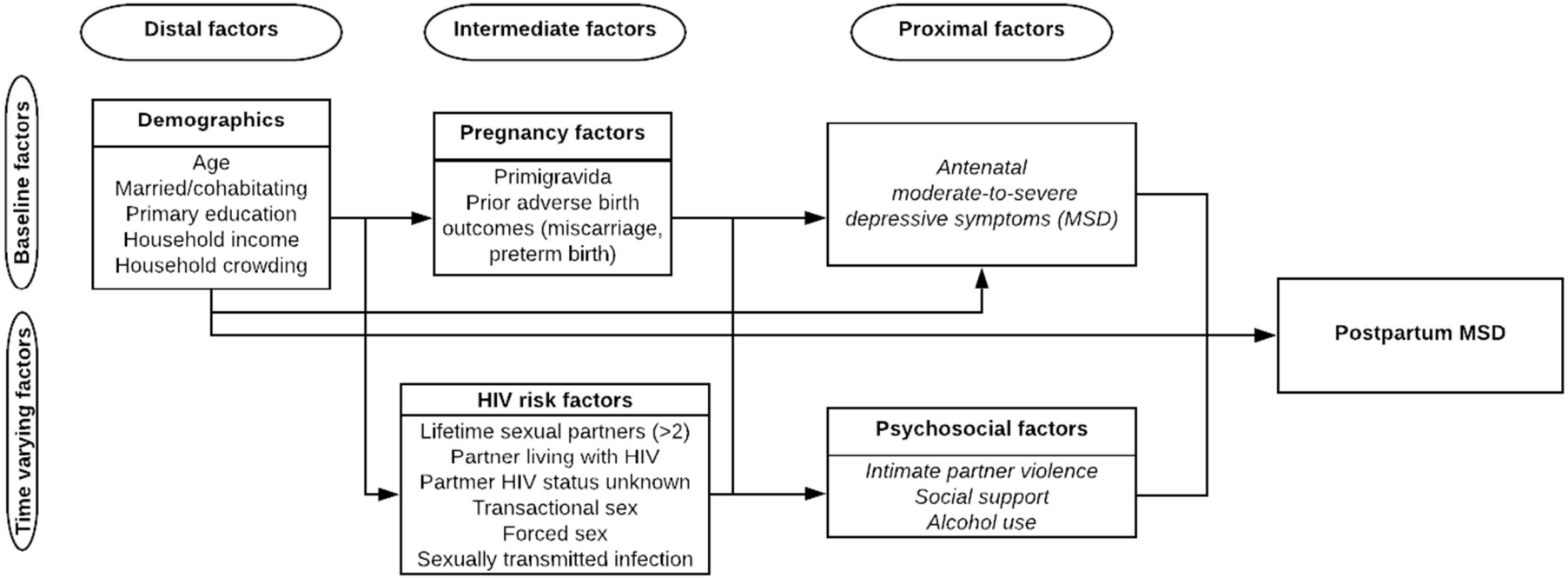
Group-based trajectory model was fit using Center for Epidemiologic Studies Depression Scale (CESD-10) as a continuous score (range 0-30), modelled as censored normal distribution, over time since enrollment (days), and time-varying covariates (Intimate Partner Violence, Low social support)

Figure 4.4. Predictors of trajectory membership: results from multivariable multinomial logistic regression with GBTM groups



Appendix

Conceptual model for perinatal depressive symptoms and cofactors

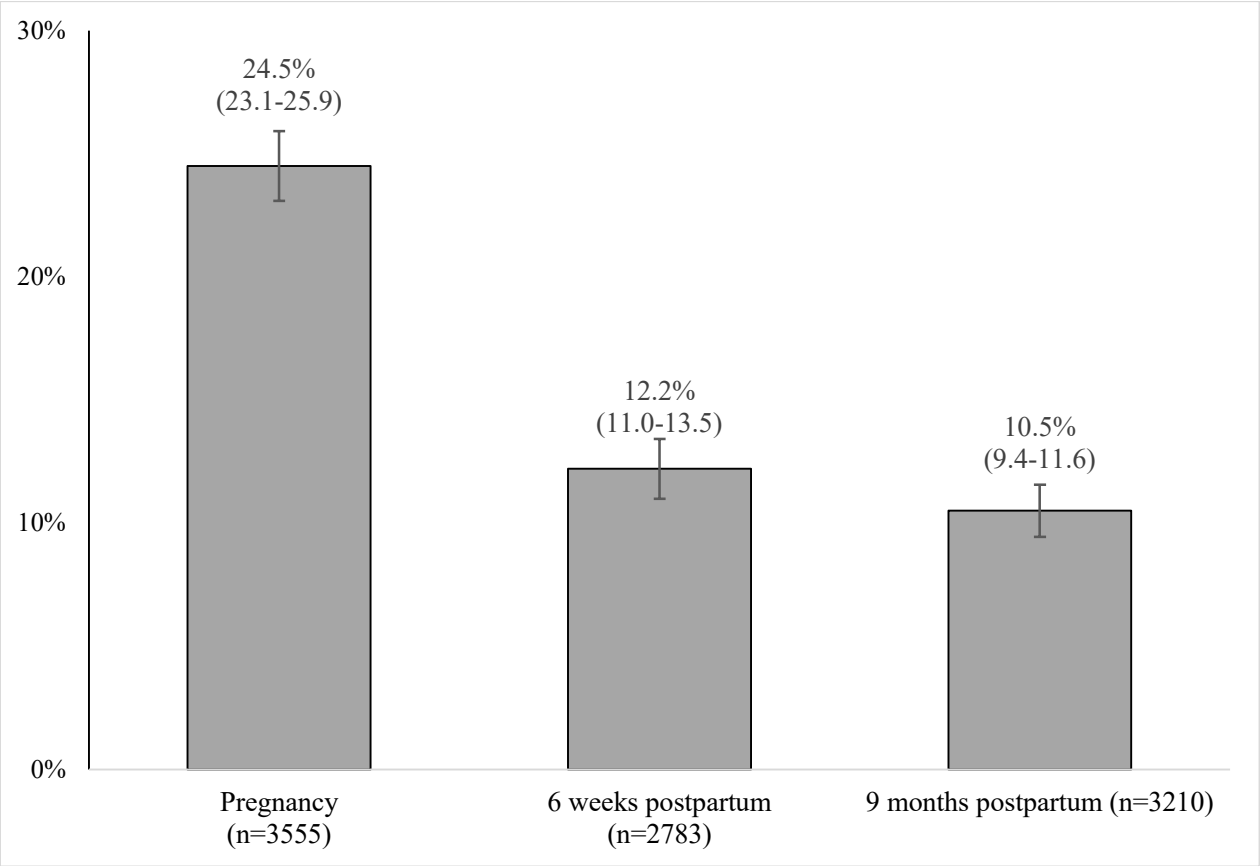


Differences between women with depressive symptom information in pregnancy only, not postpartum

	Depressive symptom information in pregnancy and postpartum (included in analysis)		Depressive symptom data in pregnancy only (not included in analysis)		
Characteristics	**N**	**n (%)**	**N**	**n (%)**	**p-value**
Age (years)	3553	24.0 (21.0, 28.7)	327	23.1 (20.3, 27.0)	0.006
Gestational age at enrollment (weeks)	3555	24.0 (20.0, 29.4)	327	24.0 (20.0, 30.0)	0.38
Not married or not living with a partner	3522	501 (14.2%)	324	73 (22.5%)	<0.001
Regularly employed	3515	491 (14.0%)	320	56 (17.5%)	0.084
Household crowding (>2 people/room)	3529	1725 (48.9%)	324	133 (41.0%)	0.007
Partner living with HIV	3507	144 (4.1%)	322	13 (4.0%)	0.95
High HIV risk[1]	3555	1257 (35.4%)	327	126 (38.5%)	0.25
Social support score[2]	3489	75.0 (62.0, 88.0)	321	73.0 (60.0, 88.0)	0.28
Low social support[2] (MOS-SSS score <72)	3489	1330 (38.1%)	321	130 (40.5%)	0.40
Intimate partner violence [3] (HITS score ≥10)	3550	278 (7.8%)	326	28 (8.6%)	0.63
Moderate-to-severe depressive symptoms (pregnancy)	3555	870 (24.5%)	327	83 (25.4%)	0.71

[1]We evaluated HIV risk using the Pintye et al.[169] risk score (high HIV risk: score >6 = “Yes”, score ≤6 = “No”).
[2]We evaluated social support using the 18-item Medical Outcomes Study social support score (MOS-SSS), defining low social support as scores below 72 (Low social support: MOS-SSS score score <72 = “Yes”, MOS-SSS score ≥ 72 = “No”).
[3]We evaluated intimate partner violence using the 4-item Hurt, Insult, Threaten, and Scream scale (HITS), defining intimate partner violence as scores of 10 and above (IPV: HITS score ≥10 = “Yes”, HITS score <10 = “No”).

Moderate-to-severe perinatal depressive symptoms by study visit



Among the 2438 women with depressive symptom data in all three time points, prevalence estimates were not meaningfully different. Pregnancy: 23·7% (579/2438), 6 weeks postpartum: 11·6% (284/2438), 9 months postpartum: 10·5% (255/2438). Line brackets on bar chart represent 95% confidence intervals.

Moderate-to-severe depressive symptoms during pregnancy by PrIMA study site

Facility	N	n (%)
Siaya facility 1	112	28 (25.0)
Siaya facility 2	228	38 (16.7)
Homa Bay facility 1	150	6 (4.0)
Homa Bay facility 2	177	16 (9.0)
Homa Bay facility 3	196	23 (11.7)
Siaya facility 3	200	29 (14.5
Siaya facility 4	170	54 (31.8)
Homa Bay facility 4	174	60 (34.5)
Homa Bay facility 5	179	119 (66.5)
Homa Bay facility 6	178	40 (22.5)
Homa Bay facility 7	176	40 (22.7)
Siaya facility 6	215	20 (9.3)
Homa Bay facility 8	218	83 (38.1)
Homa Bay facility 9	234	59 (25.2)
Siaya facility 6	80	25 (31.3)
Siaya facility 7	197	21 (10.7)
Homa Bay facility 10	167	30 (18.0)
Siaya facility 8	158	91 (57.6)
Siaya facility 9	209	18 (8.6)
Siaya facility 10	137	70 (51.1)
Total	3555	870 (24.5)

Correlates of MSD during pregnancy and predictors of postpartum MSD compared to no MSD ever from multivariable GEE models

	Pregnancy (n=3041)			Postpartum (n=2567)		
	Multivariable GEE Analysis[1]			Multivariable GEE Analysis[2]		
	aPR	**95% CI**	**p**	**aRR**	**95% CI**	**p**
Baseline factors						
Age (years)	1·00	0·99-1·01	0·749	**1·03**	**1.01-1·05**	**0·007**
Completed education (years)	1·01	0·99-1·02	0·535	**1·04**	**1.00-1·08**	**0·040**
Household crowding (>2 people/room)	**1·14**	**1·01-1·29**	**0·041**	0.98	0·78-1·23	0·834
Not married/living with a partner	**1·41**	**1·03-1·91**	**0.030**	1·33	0·95-1.84	0·095
Gestational age at enrollment (weeks)	1·01	0·99-1·02	0·330			
Multiparous	1·06	0·89-1·26	0·518			
Prior pregnancy loss	1·14	0·95-1·38	0·165	1·21	0·88-1·66	0·243
Lifetime sexual partners ≥ 2	**1·36**	**1·11-1·66**	**0·003**	**1·42**	**1.01-2·00**	**0·044**
Partner HIV-positive	**1·48**	**1·09-2.00**	**0·012**			
Partner HIV status unknown	**1·30**	**0.91 -1·85**	0·143			
Sexually transmitted infection	**1·30**	**0·99-1·70**	**0·057**			
Transactional sex	1·19	0·81-1·75	0·370			
Forced sex	1·12	0·72-1·74	0·619			
Ever drinks alcohol	1·09	0·72-1·65	0·682	1·30	0.84-2.01	0·232
Low social support (MOS-SSS score <72)	**1·77**	**1·19-2.64**	**0·005**			
Intimate partner violence[a] (HITS score ≥10)	**1·84**	**1·44-2·35**	**<0·001**			
Time-varying factors						
Intimate partner violence[b]				**2.47**	**1.72-3.56**	**<0·000**
Low social support				**2.83**	**2.30-3.49**	**<0·001**
Time since delivery (days)				1·00	1·00-1·00	0·893

[1]We estimated adjusted Prevalence Ratios (aPR) from a multivariable generalized estimating equation (GEE) with a Poisson family, log link, and independent correlation structure, clustered by facility with outcome of MSD in pregnancy (Y/N); Independent variables: Age (years), Not married/living with a partner (Y/N), Completed education (years), household crowding (Y/N), Gestational age at enrollment (Y/N), Multiparous (Y/N), Prior pregnancy loss (Y/N), Lifetime sexual partners >2 (Y/N), Partner living with HIV (Y/N), Partner HIV status unknown (Y/N), Transactional sex (Y/N), Forced sex (Y/N), Sexually transmitted infection (Y/N), Ever drinks alcohol (Y/N), Low social support (Y/N), IPV (Y/N).

[2] We estimated adjusted Relative Risks (aRR) from a multivariable generalized estimating equation (GEE) with a Poisson family, log link, and independent correlation structure, clustered by participant with outcome of MSD in postpartum only (Y/N); Independent variables: Age (years), Not married/living with a partner (Y/N), Completed education (years), household crowding (Y/N), Prior miscarriage (Y/N), Lifetime sexual partners >2 (Y/N), Ever drinks alcohol (Y/N), , low social support (time-varying [current visit], Y/N), intimate partner violence (time-varying [current visit], Y/N), time since delivery (days).

[a]We evaluated social support using the 18-item Medical Outcomes Study social support score (MOS-SSS), defining low social support as scores below 72 (Low social support: MOS-SSS score score <72 = "Yes", MOS-SSS score ≥ 72 = "No")

[b]We evaluated intimate partner violence using the 4-item Hurt, Insult, Threaten, and Scream scale (HITS), defining intimate partner violence as scores of 10 and above (IPV: HITS score ≥10 = "Yes", HITS score <10 = "No"

Model selection process for selected group-based trajectory model for perinatal depressive symptoms among Kenyan women

	Bayesian Information Criterion (BIC)	Akaike Information Criterion (AIC)	Log Likelihood (LL)
Step 1: Identifying number of trajectory groups by best-fit model[1]			
Two trajectory groups	-26900.7	-26851.4	-26835.4
Three trajectory groups	-26867.0	-26793.0	-26769.0
Four trajectory groups	-26747.1	-26648.4	-26616.4
Five trajectory groups[2]	-26720.4	-26597.1	-26557.1
Step 2: Identifying polynomial form of each trajectory group by best-fit model[2]			
Model selected based on BIC value: Group 1 ("no depressive symptoms): linear Group 2: ("Resolving MSD") quadratic Group 3: ("Chronic mild symptoms") quadratic Group 4: ("Persistent MSD") cubic Group 5: ("Emergent MSD") cubic	-26648.8	-26525.5	-26485.5

[1]We compared BIC for each of the four models in Step 1 and selected the 5-trajectory model since it had the most optimal BIC value. All trajectory groups were initially modeled using cubic polynomials. We used the extension for non-random attrition to relax assumptions of missingness completely at random.

[2]We ran all model permutations for 5-trajectories with polynomial forms (linear – quadratic) and selected the best fitting model using BIC. We used the extension for non-random attrition to relax assumptions of missingness completely at random.

Model adequacy characteristics for selected group-based trajectory model for perinatal depressive symptoms among Kenyan women

	Group 1: "no depressive symptoms" n=372	**Group 2: "Resolving MSD"** n=139	**Group 3: "Chronic mild symptoms"** n=2709	**Group 4: "Persistent MSD"** n=295	**Group 5: "Emergent MSD"** n=40
Proportion in each group based on assignments for maximum posterior probability[1]	10.46%	3.91%	76.20%	8.30%	1.13%
Expected proportion in each group based on sums of posterior probabilities[1]	13.14 %	4.75%	71.65%	9.30%	1.16%
Average posterior probabilities[2]	71.88%	77.07%	87.90%	78.32%	90.83%

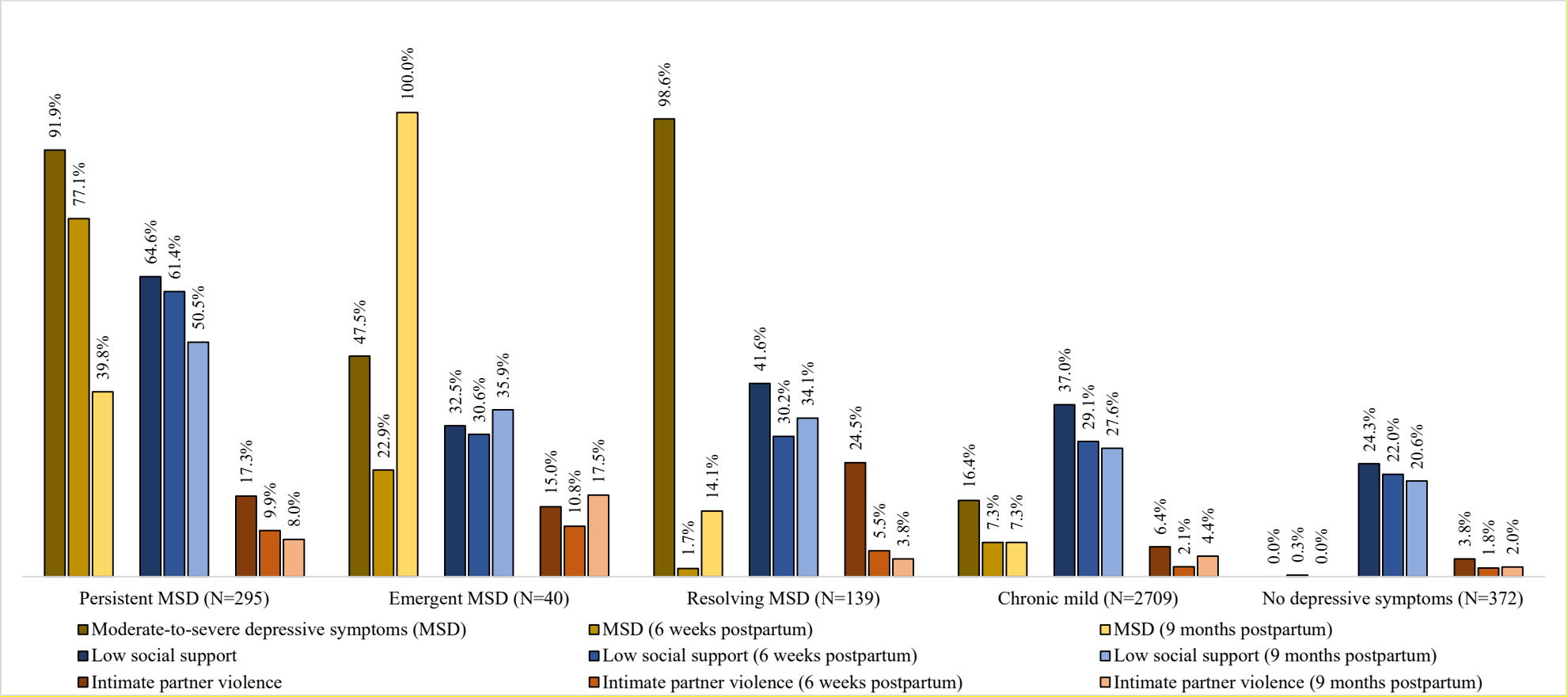
[1]We achieved model adequacy since the proportion based on maximum posterior probability and expected proportion based on sums of posterior probabilities are within <5% of each other.
[2]We achieved model adequacy since average posterior probability in each group was ≥70%.

Predictors of perinatal depressive symptoms trajectory group membership: results from multivariable multinomial logistic regression

	Emergent MSD vs. No depressive symptoms (n=40)			Resolving MSD vs. No depressive symptoms (n=139)			Persistent MSD vs. No depressive symptoms (n=295)		
	aOR[1]	**95% CI**	**P**	**aOR**	**95% CI**	**p**	**aOR**	**95% CI**	**p**
Older adults (>24 years)	**2·2**	**1·1-4·4**	**0·034**	1·1	0·7-1·7	0·593	1·3	0·9-1·8	0·168
Not married/living with a partner	2·2	0·8-5·8	0·122	2·5	**1·4-4·5**	**0·001**	1·6	1.0-2.6	0·065
Household crowding	0.8	0·4-1·5	0·456	1·6	1·1-2·4	0·024	1·3	0·9-1·8	0·133
High HIV risk	1·0	0·5-2·1	0·902	**1·7**	**1·1-2·6**	**0·010**	**1·8**	**1·3-2·5**	**0·001**
Prior pregnancy loss	1·6	0·6-4·1	0·340	1·7	0·9-3·1	0·095	**1·9**	**1·2-3·1**	**0·011**
Low social support	1·4	0·7-2·8	0·366	**1·9**	**1·3-2·9**	**0·003**	**5·3**	**3·8-7·5**	**<0·001**
Intimate partner violence	**4·0**	**1·4-11·4**	**0·009**	**6·2**	**3·1-12·3**	**<0·001**	**3·5**	**1·8-6·5**	**<0·001**

[1]We estimated adjusted odds ratios (aOR) from a multivariable multinomial logistic regression model with outcome: trajectory groups from group-based trajectory model; independent variables: older age (>24 years) (Y/N), Not married/living with a partner (Y/N), Household crowding (Y/N), High HIV risk (Y/N), Prior pregnancy loss (Y/N), Low social support (Y/N), Intimate partner violence (Y/N).

Profiles of perinatal depressive symptom group members



	Persistent MSD			Emergent MSD			Resolving MSD			Chronic mild			No depressive symptoms		
	Median (IQR)			Median (IQR)			Median (IQR)			Median (IQR)			Median (IQR)		
CESD-10 Scores	**Preg.**	**6 weeks**	**9 months**	**Preg.**	**6 weeks**	**9 months**	**Preg.**	**6 weeks**	**9 months**	**Preg.**	**6 weeks**	**9 months**	**Preg.**	**6 weeks**	**9 months**
Among all members	**14 (12-17)**	**12 (10-16)**	**8 (5-11)**	**9 (3-12)**	**3 (0-9)**	**22 (20-27)**	**19 (17-22)**	**2 (0-5)**	**3 (0-7)**	**5 (3-8)**	**4 (3-6)**	**3 (2-6)**	**0 (0-1)**	**0 (0-1)**	**0 (0-0)**
Among members with MSD	**14 (12-18)**	**13 (12-17)**	**12 (11-14)**	**12 (11-14)**	**13 (10-18)**	**22 (20-27)**	**19 (17-22)**	**11 (10-12)**	**11 (10-13)**	**11 (10-12)**	**11 (10-13)**	**11 (10-13)**	**0 (0-0)**	**10 (10-10)**	**0 (0-0)**

Chapter 5: Perinatal depression and correlates among Kenyan women living with HIV

Chapter 5a: Antenatal depressive symptoms in Kenyan women living with HIV

Antenatal depressive symptoms in Kenyan women living with HIV: contributions of recent HIV diagnosis, stigma, and partner violence

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Abstract
Depression among pregnant women living with HIV (WLWH) in sub-Saharan Africa (SSA) leads to poor pregnancy and HIV outcomes. This cross-sectional analysis utilized enrollment data from a randomized trial (Mobile WAChX, NCT02400671) in 6 Kenyan public maternal and child health clinics. Depressive symptoms were assessed with the Patient Health Questionnaire-9 (PHQ-9), stigma with the Stigma Scale for Chronic Illness, and intimate partner violence (IPV) with the Abuse Assessment Screen. Correlates of moderate-to-severe depressive symptoms (MSD, PHQ-9 score $\geq$10) were assessed using generalized estimating equation models clustered by facility. Among 824 pregnant WLWH, 9% had MSD; these women had more recent HIV diagnosis than those without MSD (median 0.4 versus 2.0 years since diagnosis, p=0.008). MSD was associated with HIV-related stigma (adjusted Prevalence Ratio [aPR]:2.36, p=0.025), IPV (aPR:2.93, p=0.002), lower social support score (aPR:0.99, p=0.023), and virologic failure (≥4 months since antiretroviral therapy exposure, aPR:1.8, p=0.007). Using population-attributable risk percent to estimate contributors to maternal depression, 81% were attributable to stigma (27%), recent diagnosis (24%), and IPV (20%). Integrating depression screening and treatment in prevention of mother-to-child HIV transmission programs may be beneficial, particularly in women recently diagnosed or reporting stigma and IPV.

Keywords: Depression, pregnancy, HIV, women, Kenya, Sub-Saharan Africa

Introduction

Depression during pregnancy is the most common complication of childbearing, affecting one in ten pregnant women worldwide [19,78,79], which is elevated from 4% prevalence among the general population (World Health Organization, 2017). Changes in reproductive and stress hormones during pregnancy influence depressive symptoms, as do genetic factors, prior adverse life experiences, history of depression or anxiety, lack of social support, and other stressors [13,81–84]. Depression in pregnancy may negatively influence fetal development [181], and increases the risk of adverse pregnancy outcomes such as preterm birth and low infant birthweight [32,182–185]. The burden of antenatal depression is particularly high in low- and middle-income countries (LMICs) where a quarter of childbearing women suffer from depression [19,42].

Beyond the influence of pregnancy-related physical and social changes on mental health, comorbid health conditions like HIV also increase depressive symptoms. People living with HIV (PLWH) experience five times the frequency of depression than the general population [179] and women living with HIV (WLWH) are even more burdened, with up to one third depressed [186]. Depression risk may be elevated among PLWH through psychosocial influences, including HIV-related stigma, isolation, or HIV-associated disability, as well as through biological pathways resulting from HIV infection [187]. Depression among PLWH negatively impacts adherence to HIV care and treatment [188], which may prevent viral suppression, increasing disease progression and risk of mother-to-child transmission of HIV [189–191].

For pregnant WLWH, the effects of both pregnancy and HIV-infection compound to make this group particularly vulnerable to antepartum depression, especially in LMICs of SSA, where pregnancy, depression, and HIV infection are common and access to mental health services is limited [191–194]. A few studies have estimated the prevalence of depression during pregnancy among WLWH in SSA, finding substantial depressive symptoms among this group [63]. However, gaps remain in our understanding of who is most at risk for antenatal depression and the

magnitude of influence of associated cofactors. To contribute to filling these gaps, we evaluated the prevalence and correlates of depression, as well as the population attributable risk percent (PAR %) of those correlates on depression among pregnant WLWH in Kenya.

Methods

Study design

This was a cross-sectional analysis of baseline data from the Mobile WAChX study, a randomized controlled trial (RCT) conducted at 6 maternal and child health (MCH) clinics in the Nairobi and Nyanza regions of Kenya (clinical trial NCT02400671) [77]. Nairobi study sites were Mathare and Riruta Health Centres; Nyanza sites were Ahero, Rachuonyo, Siaya County and Bondo sub-county Hospitals. The RCT compares the impact of 1-way SMS, 2-way SMS and control (no SMS) on antiretroviral therapy (ART) adherence, viral suppression and retention in care among pregnant and postpartum women receiving Option B+ prevention of mother-to-child HIV transmission (PMTCT) services.

Study participants

Women were eligible to participate in the study if they were pregnant (any gestational age), HIV-infected, aged ≥14 years, receiving MCH and HIV care at the study clinic, had daily access to a mobile phone, and were not participating in another research study. All women who attended antenatal care (ANC) at study clinics between November 2015 and May 2017 were screened for study eligibility.

Data collection procedure and measures

This analysis used data collected at study enrollment. Data were collected using a tablet-based Open Data Kit questionnaire administered by a study nurse in either English, Kiswahili, or Dholuo. The questionnaire ascertained demographic characteristics and psychosocial factors including depressive symptoms, HIV-related stigma, social support, and intimate partner violence (IPV).

We assessed depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) screening scale which asks respondents to indicate “not at all”, “several days”, “more than half the days”, or “nearly every day” for the frequency in the last 2 weeks that they experienced each of 9 proposed problems [195,196]. Each ranked response corresponds to a score 0-3, and higher total scores describe higher severity of depressive symptoms (range: 0-27). We defined “moderate-to-severe depressive symptoms” (MSD) as PHQ-9 score ≥10 and compared those with MSD to those without MSD (PHQ-9 score <10).

We evaluated HIV-related stigma using a 4-question version of the Stigma Scale for Chronic Illness (SSCI) among participants who had been diagnosed with HIV prior to enrollment [197,198]. Respondents indicate whether they agree with the following statements: “Because of my illness, some people avoided me”, “Some people acted as though it was my fault I have this illness”, “Because of my illness, I felt left out of things”, “I felt embarrassed about my illness”. We defined endorsement of any items as experience of any stigma, endorsement of embarrassment or feeling left out as internalized stigma, and experience of being avoided or faulted as enacted stigma. Due to a data collection error, stigma questions were not asked of all eligible women in the study. Social support was assessed using the Medical Outcomes Study (MOS) survey social support scale, where respondents identify how often they are able to elicit support for various scenarios and higher scores indicate higher social support (range: 18-90) [151]. We administered the Abuse Assessment Screen to participants to evaluate IPV [199], and defined experience of IPV in the last 12 months as a response of “yes” to the question, “Within the last 12 months, have you been hit, slapped, kicked, or otherwise physically hurt by someone in the past year?” Clinical data including plasma HIV viral load (VL) and ART initiation date were abstracted from patient files at the study clinic. Viral failure was categorized as having a VL ≥1000 copies/ml after being on ART for at least 4 months.

Statistical methods

We used descriptive statistics to determine the prevalence of MSD symptoms. Chi-squared tests were used to compare binomial or categorical demographic and psychosocial characteristics and t-tests to compare continuous variables across levels of depressive symptoms. Correlates of MSD were assessed using univariable and multivariable generalized estimating equation models (GEE) with Poisson link and exchangeable correlation structure clustered by facility. This approach was used to account for potential within-facility correlation contributing to differences in outcome frequency (Supplementary Table 1). Variables with p-value ≤0.1 in univariable analysis were considered for inclusion in multivariable analyses. Three multivariable analyses were conducted. The first included variables significant at p-value ≤0.1 that had complete information from all study participants (unintended pregnancy, HIV diagnosis within the prior 2 years, IPV, social support score). The second model included those participants with data on HIV-related stigma, and evaluated the association between HIV-related stigma and MSD, adjusted for unintended pregnancy, HIV diagnosis within the prior 2 years, IPV, and social support score. In the third model, we hypothesized that virologic failure as an outcome may be influenced by MSD as an exposure, thus we evaluated virologic failure as the dependent variable with MSD as the main independent variable of interest, adjusted for unintended pregnancy, HIV diagnosis within the prior 2 years, IPV, and social support score. We estimated PAR% from adjusted effect sizes of dichotomous factors significantly associated with MSD at p-value ≤0.1 in multivariable models. Analyses were conducted using Stata version 15.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

Ethical approval was obtained from the University of Washington and Kenyatta National Hospital/University of Nairobi institutional review boards. The study was performed in accordance

with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

All participants gave written informed consent in their preferred language (Kiswahili, English, or Dholuo) prior to participating in the study. Pregnant women age 14 or older are emancipated by pregnancy according to local regulations and guidelines and were able to provide consent independently.

Results

Overall, 824 pregnant WLWH were recruited from the 6 study sites. The median age was 27 years (interquartile range [IQR] 23-31), 115 (14%) were primigravida, and about half (452, 55%) had intended pregnancies (Table 5a.1). Most women (694, 84%) were married or cohabiting, and over three quarters (633, 77%) reported completion of at least primary education. The median time since HIV diagnosis was 2 years (IQR 0.1-5.0), most participants (660, 80%) had disclosed their HIV status to another person, 183 (41%) reported experiencing any HIV-related stigma, and 92 women (11%) reported IPV in the last 12 months.

One in 10 women (71, 9%) had MSD; about one third had at least mild depressive symptoms (PHQ-9 score ≥5, 30%). Prevalence of MSD differed between study sites ranging from <1% to 35% (Supplementary Table 5a.1). To determine correlates of MSD among pregnant WLWH, we compared frequency of MSD by levels of multiple demographic, partnership, and psychosocial characteristics. We contextualized potential correlates within a conceptual model to ground hypothesized relationships as distal, intermediate, and proximal factors contributing to MSD in this group (Figure 5a.1). This model was adapted from Pearlin and colleagues' 1981 conceptual model for the stress process [200] and the Leigh and Milgrom [201] conceptual model for risk factors for peripartum depression.

Demographic factors: Maternal age, educational attainment, marital status, household income, and household crowding were considered distal factors; we found no statistically significant relationships between these characteristics and MSD (Table 5a.2).

HIV-related factors: We hypothesized that HIV-related factors would function as intermediate influencers in the pathway leading to antenatal MSD. Pregnant WLWH diagnosed with HIV within the last 2 years had 70% higher frequency of MSD compared to those who had received their HIV diagnosis more than two years ago (prevalence ratio [PR]: 1.68 [1.01-2.80]) (Table 5a.2). This effect size remained after adjustment for potential confounders (adjusted PR [aPR]: 1.67 [0.99-2.78], p-value: 0.05). Pregnant women who experienced any type of HIV-related stigma had nearly three times the frequency of MSD than those not reporting stigma (PR: 2.70 [1.16-6.34]) and this effect was maintained after adjustment (aPR: 2.36 [1.11-5.01]). When deconstructed into “enacted” and “internalized” stigma, we found that both domains were associated with MSD. Those experiencing enacted stigma had double the frequency of MSD (PR: 1.99 [1.17-3.39]) compared to those not experiencing enacted stigma. Those experiencing internalized stigma had 2.5-times the frequency of MSD (PR: 2.48 [1.27-3.39]) compared to those without internalized stigma. Disclosure of one’s HIV status to another person was not associated with MSD among this population.

Pregnancy-related factors: We also conceptualized pregnancy-related factors as intermediate influencers of MSD. Women who indicated their current pregnancy was unintended experienced MSD at 30% higher frequency than those reporting the pregnancy was intended (PR: 1.27 [1.01-1.59]). When adjusted for potential confounders, this effect was not sustained (aPR: 1.24 [0.94-1.62], p=0.13). Other pregnancy-related factors (gestational age, primigravida) were not associated with MSD.

Psychological factors: IPV and social support were conceptualized as those most proximal to antenatal MSD among this population. Correspondingly, we found women who had experienced violence from a partner within the last year had over three times the frequency of

MSD compared to those not reporting IPV (PR: 3.11 [1.66-5.83]). This large effect size was sustained after confounding adjustment (aPR: 2.93 [1.49-5.75]). Further, pregnant WLWH with MSD had lower social support scores than those without MSD (55 [IQR: 36-66] versus 64 [IQR: 51-72], p<0.001), which remained in multivariable analysis (p=0.05).

We estimated PAR% of each factor identified as a correlate of MSD in univariable analysis, finding that 37% of MSD cases among this population of pregnant WLWH were attributable to experiencing HIV-related stigma (PAR%: 37.1 [-1.2-61.1]). The correlate with the next highest attributable risk for MSD was HIV diagnosis within the last two years, accounting for 24% of MSD cases among this population (PAR%: 24.5 [-3.1-44.7]). About 20% of MSD burden was due to IPV within the last year [PAR%: 19.6 [2.3-33.7]).

Potential effects of MSD on viral suppression: Among pregnant women who had been on ART for at least 4 months, we observed a trend for the association between MSD and viral non-suppression, where those experiencing VL ≥1000 copies/ml had twice the frequency of MSD than those virally suppressed (VL <1000 copies/ml) (PR: 2.01 [0.92-4.42], p=0.08), and this effect was sustained and became statistically significant in multivariable analysis (aPR: 1.80 [1.18-2.76], p=0.01).

Discussion

In this study of Kenyan pregnant WLWH attending ANC, one in ten demonstrated MSD. Depression was associated with recent HIV diagnosis (within the prior two years), experiencing HIV-related stigma, IPV within the past year, and lower social support. Among women on ART for at least 4 months, MSD was associated with viral non-suppression.

The prevalence of 10% for MSD and 30% mild or higher depressive symptoms observed in our study is consistent with previous studies among pregnant WLWH [63,191,202–207], though studies differ in the scale used to assess depression, making direct comparisons challenging. WLWH in SSA experience high levels of psychosocial and socioeconomic adversity, which may be exacerbated by hormonal changes experienced during pregnancy and the stressors

associated with caring for a newborn [208,209]. Our analysis adds to the sparse literature about antenatal depression among WLWH in SSA and supports previous reports that peripartum women in these regions have a substantial prevalence of depression [203–208,210,211].

Our conceptual model contextualized factors assessed for their relationship with antenatal depressive symptoms into categories of demographics, HIV-related factors, pregnancy-related factors, and psychosocial factors. Multiple HIV-related factors were associated with MSD during pregnancy among this population of WLWH. We found a significant association between depressive symptoms and experience of HIV-related stigma, an association also observed in other studies in SSA [197,212,213]. Experiencing HIV-related stigma accounted for the highest PAR% for MSD among this cohort of pregnant WLWH, compared to other factors associated with MSD. Efforts to normalize HIV diagnosis and reduce societal stigma related to HIV could substantially reduce prevalence of antenatal depression.

We found that recent diagnosis with HIV within the past two years was significantly associated with depression, suggesting there is a need for close monitoring and surveillance of women newly testing positive for HIV during pregnancy to detect and address depressive symptoms. Recent HIV diagnosis accounted for a quarter of MSD cases. Effective treatment of depression among pregnant women may help prevent adverse pregnancy outcomes associated with depressive symptoms such as preterm birth, low birthweight, maternal hypertension, and suboptimal infant feeding [63,209,214]. Further, we noted a significant association between antenatal depressive symptoms and the outcome of virologic non-suppression on established ART, consistent with other studies showing significant association of depression with higher VL in SSA [215,216]. This finding highlights the need for improved adherence counseling and comprehensive depression screening and treatment among this group to help in not only addressing depression, but also attaining viral suppression [215,217,218].

Experiencing a pregnancy that was not intended was associated with antenatal MSD, and about one in ten MSD cases was attributable to this pregnancy-related factor. Improving access to family planning methods and promoting their use could reduce prevalence of antenatal depression by prevention of unintended pregnancies.

Pregnant WLWH who experienced IPV in the last 12 months had a substantially higher prevalence of depression than those who did not report IPV, and one in five MSD cases were attributable to IPV. Studies in South Africa, Zimbabwe, Zambia, Tanzania, and Ethiopia similarly found that depression was elevated in participants reporting past-year physical and/or sexual IPV [211,213,219–221]. Interventions to address IPV are needed in order to holistically address maternal health, including mental health.

Our study highlights the need for mental health interventions to be integrated into routine MCH and HIV care to reduce depressive symptoms among pregnant WLWH in SSA. Potential interventions could include implementation of psychosocial support groups and counseling services for those newly diagnosed with HIV, which have been shown in SSA settings to improve psychosocial health [217,218,222,223]. Further, interventions that counteract the negative effects of HIV-related stigma may prevent or alleviate depressive symptoms [223–226]. Integration of IPV screening within routine MCH care could improve detection of IPV and allow for targeted counseling and monitoring to prevent and reduce associated depressive symptoms [219,221,227–229].

The correlates of MSD identified in this study help determine which pregnant WLWH should be prioritized for depressive symptom screening and treatment, yet a deeper understanding of these cofactors' influence on antenatal depression is required to design effective interventions. Our conceptual model further contextualizes the interconnectedness of demographic, HIV-related, pregnancy-related, and psychosocial factors which influence maternal mental health during pregnancy. Effect sizes of MSD cofactors were observed to generally increase from distal, to intermediate, to proximal factors, suggesting the potential relative influence of interventions at each stage. Further, the difference in PAR% across correlates of

MSD emphasizes the importance of considering prevalence of a cofactor within a population when designing interventions to optimize impact among prioritized high-risk groups.

Introduced in 2015, the Kenya Mental Health Policy 2015-2030 was developed with the goal of attaining the highest standard of mental health through mental health systems reform [103]. Specifically, the policy calls for integration of mental health training, records tracking and care into existing primary care settings, and calls for research focused on mental health to inform appropriate intervention. Our study provides such findings, highlighting the importance of reducing the burden of depressive symptoms among pregnant WLWH with specific focus on those reporting stigma, recently diagnosed with HIV, experiencing IPV, those with lower social support, and those experiencing VL failure. These correlates and their attributable risks to antenatal depression within this population should be used to inform interventions to alleviate depressive symptoms among pregnant WLWH in sub-SSA.

Our study has a number of limitations. As a cross-sectional study we lacked information about temporality to assess longitudinal precursors, incidence, and recurrence of depressive episodes. In the absence of available mechanisms for clinical diagnosis, we used the PHQ-9 to screen for depressive symptoms. While less definitive than diagnosis, the PHQ-9 has been validated for reliable use in diverse settings, including SSA [230–233]. We observed differences in prevalence of depressive symptoms by study site; this may represent meaningful regional differences, or it may reflect differences in administration of the PHQ-9 questions by study staff. While we are unable to determine the reason for site-level differences, we analytically accounted for clustering of the data by site by using a GEE. Despite adjusting for clustered data, residual confounding by study site may be present. In analyses adjusted for site, associations were retained (data not shown).

Conclusion

Our findings highlight the need for improved depression screening and treatment for pregnant WLWH in routine ANC, particularly those reporting HIV-related stigma, diagnosed with

HIV within the past two years, with virologic failure, with low social support, and experiencing IPV. We recommend further research on peripartum depression that utilizes longitudinal designs and development of community-based or clinical interventions to alleviate cofactors and ultimately reduce antenatal depression among WLWH.

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TABLES AND FIGURES

Table 5a.1. Sociodemographic, clinical, and behavioral characteristics of HIV-infected

	No moderate-to-severe depression		Moderate-to-Severe depression	
Characteristics	**N**	**n or median (% or IQR)**	**N**	**n or median (% or IQR)**
Depression score (PHQ-9)[a]	753	2 (0-4)	71	13 (11-15)*
Age (years)	753	27 (23-31)	71	25 (22-29)*
Gestational age (weeks)	746	24 (18-30)	71	25 (18-31)
Primigravida	753	103 (13.7)	71	12 (16.9)
Pregnancy intended	750	421 (56.1)	71	31 (43.6)*
Primary education completed	753	582 (77.3)	71	51 (71.8)
Married/cohabiting	753	638 (84.7)	70	56 (80.0)
Monthly household income (USD)	493	80 (40-150)	34	55 (30-120)
Household crowding (≥3/room)	753	273 (36.3)	71	17 (23.9)*
Time since HIV diagnosis (years)	749	2.0 (0.1-5.0)	71	0.4 (0.04-3.2)*
HIV status disclosed to anyone	737	609 (82.6)	69	51 (73.9)
Any stigma reported [b]	406	152 (37.4)	45	31 (68.9)*
Enacted stigma	406	47 (11.6)	45	13 (28.9)*
Internalized stigma	406	139 (34.2)	45	28 (62.2)*
IPV in the last 12 months[c]	753	69 (9.2)	71	23 (32.4)*
Social support score[d]	753	64 (51-72)	71	55 (36-66)*
VL (log_{10} copies) ≥4 months since ART initiation	439	1.3 (1.3-1.7)	33	2.1 (1.3-3.0)*
VL ≥1000 copies/ml ≥4 months since ART initiation	439	45 (10.3)	33	10 (30.3)*

[a] 27-point scale, [b]Stigma Scale for Chronic Illness (Any stigma = any scale item endorsed, Enacted = "Because of my illness, some people avoided me" or "Some people acted as though it was my fault I have this illness" endorsed, Internalized = "I felt embarrassed about my illness" or "Because of my illness, I felt left out of things" endorsed), [d]72-point scale, *P-values <0.05 from chi-squared tests for binary or categorical characteristics, t-tests for continuous characteristics; PHQ-9: patient health questionnaire-9, HIV: human immunodeficiency virus, VL: viral load, IPV; intimate partner violence, IQR: interquartile range

Table 5a.2. Correlates of moderate-to-severe depressive symptoms among pregnant women living with HIV

	MSD	No MSD	MSD vs No MSD						PAR %	
	N (%)	N (%)	PR	95% CI	p-value	aPR	95% CI	p-value	PAR %[d]	95% CI
Adolescent (≤19 years old)										
No	66 (8.3)	725 (91.7)	ref							
Yes	5 (15.2)	28 (84.9)	1.56	(0.43-5.71)	0.50					
Gestational age (weeks)										
No	34 (8.5)	367 (91.5)	ref							
Yes	37 (8.8)	386 (91.3)	0.93	(0.71-1.21)	0.59					
Primigravida										
No	59 (8.3)	650 (91.7)	ref							
Yes	12 (10.4)	103 (89.6)	1.22	(0.83-1.79)	0.31					
Pregnancy unintended										
No	31 (6.9)	421 (93.1)	ref			ref				
Yes	40 (10.8)	329 (89.2)	1.27	(1.01-1.59)	0.04	1.24[a]	(0.94 – 1.62)	0.13		
Primary education completed										
No	20 (10.5)	171 (89.5)	ref							
Yes	51 (8.06)	582 (91.9)	0.93	(0.54-1.59)	0.79					
Married/cohabiting										
No	14 (10.9)	115 (89.2)	ref							
Yes	56 (8.1)	638 (91.9)	0.81	(0.42-1.59)	0.55					
Household income above median (≥80 USD)										
No	13 (4.87)	254 (95.1)	ref							
Yes	21 (8.1)	239 (91.9)	0.94	(0.58-1.54)	0.82					
Household crowding (≥3/room)										
No	54 (10.1)	480 (89.9)	ref							
Yes	17 (5.9)	273 (94.1)	0.88	(0.65-1.20)	0.41					
HIV diagnosis <2 years ago										
No	27 (6.3)	404 (93.7)	ref			ref				
Yes	44 (11.3)	345 (89.7)	1.68	(1.01-2.80)	0.05	1.67[a]	(0.99-2.78)	0.05	24.46	(-3.07-44.65)
Disclosed to anyone										
No	18 (12.3)	128 (87.7)	ref							
Yes	51 (7.7)	609 (92.3)	0.72	(0.40-1.27)	0.26					
IPV in the last 12 months										
No	48 (6.6)	684 (93.4)	ref			ref				
Yes	23 (25.0)	69 (75.0)	3.11	(1.66-5.83)	<0.001	2.93[a]	(1.49-5.75)	0.002	19.55	(2.33-33.73)
Social support score	64 (51-72)	55 (36-66)	0.99	(0.97-1.00)	0.02	0.99[a]	(0.98-1.00)	0.05		
Any stigma reported										
No	14 (5.2)	254 (94.8)	ref			ref				
Yes	31 (16.9)	152 (83.1)	2.70	(1.16-6.34)	0.02	2.36[b]	(1.11-5.01)	0.03	37.07	(-1.91-61.14)
Enacted stigma										
No	32 (8.2)	359 (91.8)	ref							
Yes	13 (21.7)	47 (78.3)	1.99	(1.17-3.39)	0.01					
Internalized stigma										
No	17 (5.9)	267 (94.0)	ref							

Yes	28 (16.8)	139 (83.2)	2.48	(1.27-4.84)	0.01			
VL ≥1000 copies/ml ≥4 months since ART initiation								
No	23 (5.52)	394 (94.5)	ref			ref		
Yes	10 (18.2)	45 (81.8)	2.07	(0.91-4.72)	0.08	1.80[c]	(1.18-2.76)	

MSD: Moderate-to-severe depressive symptoms (PHQ-9 score ≥10); PR: Prevalence ratio; aPR: adjusted Prevalence Ratio; PAR %: Population Attributable risk percent

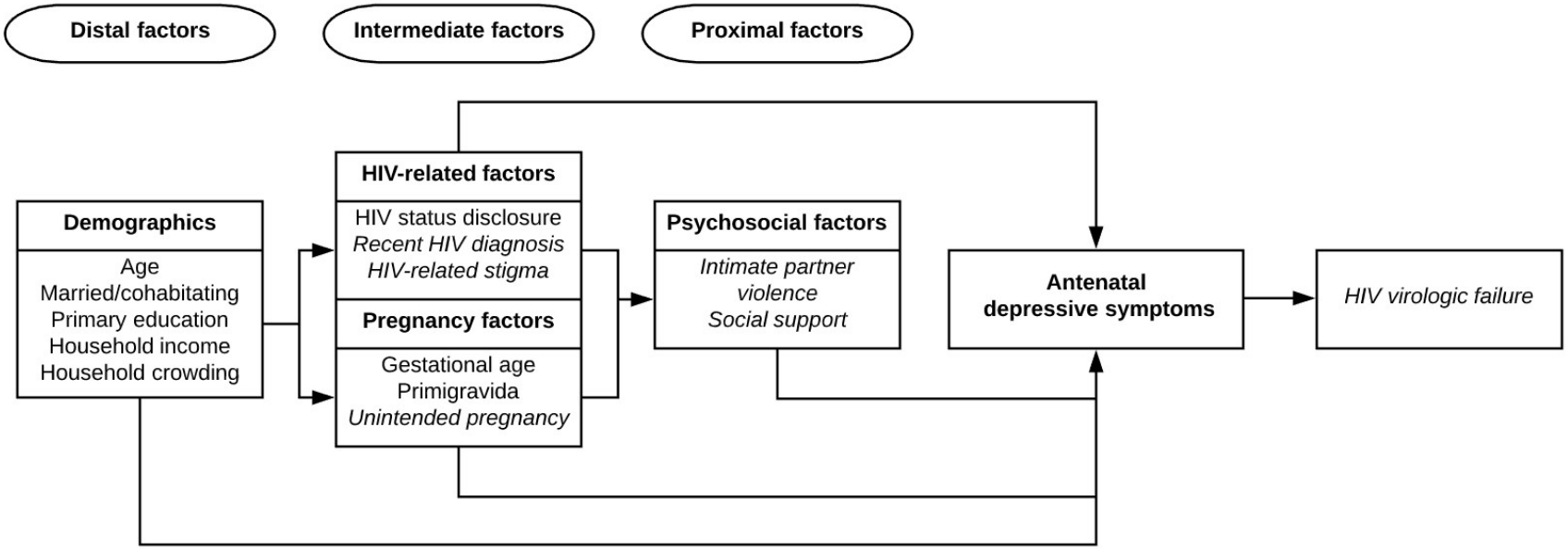
[a] Dependent variable: MSD; Independent variables: unintended pregnancy, HIV diagnosis (<2 years vs. ≥2 years), intimate partner violence, social support score

[b] Dependent variable: MSD; Independent variables: unintended pregnancy, HIV diagnosis (<2 years vs. ≥2 years), intimate partner violence, social support score, any stigma reported

[c] Dependent variable: virologic failure (>1000 copies/ml, ≥4 months since ART initiation failure); Independent variables: MSD, unintended pregnancy, HIV diagnosis (<2 years vs. ≥2 years), intimate partner violence, social support score, any stigma reported

[d] PAR % estimated from adjusted PRs for dichotomous factors associated with MSD at p-value ≤ 0.1

Figure 5a.1. A conceptual framework for correlates of antenatal depression among women living with HIV (adapted from Pearlin et al. and Leigh & Milgrom)



Italics indicate factor was associated with moderate to severe depressive symptoms (MSD) at alpha=0.1 in univariable analyses

APPENDIX

Supplementary Table 1. Prevalence of moderate-to-severe depressive symptoms by site

Clinic	N	Moderate-to-severe depression	
	824	n	%
Western Kenya clinic 1	164	1	0.6
Western Kenya clinic 2	171	4	2.3
Western Kenya clinic 3	63	7	11.1
Western Kenya clinic 4	120	42	35.0
Nairobi clinic 1	228	14	6.1
Nairobi clinic 2	78	3	3.9

Chapter 5b: Trajectories of depression symptoms from pregnancy through 24 months postpartum among Kenyan women living with HIV

Trajectories of depression symptoms from pregnancy through 24 months postpartum among Kenyan women living with HIV

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ABSTRACT

Background: We examined longitudinal patterns and cofactors of depressive symptoms among pregnant and postpartum women living with HIV (WLWH).

Methods: This study utilized data from a randomized trial of a text messaging intervention. WLWH were serially assessed for depressive symptoms from pregnancy through 24 months postpartum at 6 timepoints (pregnancy; 6 weeks; 6, 12, 18, 24 months postpartum). Depressive symptoms were assessed using Patient Health Questionnaire-9 (PHQ-9) and longitudinal patterns using group-based trajectory modeling. Moderate-to-severe depressive symptoms (MSD) correlates were assessed using generalized estimating equations.

Results: Among 824 enrolled women, 14.6% ever had MSD during pregnancy or postpartum; 8.6% of WLWH had MSD in pregnancy and 9.0% any postpartum MSD. MSD was associated with abuse (RR:3.8, 95% CI:2.6-5.4), stigma (RR:4.4, 95% CI:3.1-6.3), and food insecurity (RR:2.7, 95% CI:1.9-3.8). Unintended pregnancy (RR:1.6, 95% CI:1.1-2.3) and recent HIV diagnosis (RR:1.8, 95% CI:1.2-2.6) were associated with higher MSD risk while HIV status disclosure to partner (RR:0.3, 95% CI:0.2-0.6) and social support (RR:0.97, 95% CI:0.96-0.98) were associated with lower risk. Trajectory modeling identified 4 phenotypes of peripartum depressive symptoms: persistent no/low symptoms (38.5%), mild symptoms resolving postpartum (12.6%), low symptoms increasing slightly in postpartum (47.9%), and persistent moderate-severe symptoms throughout (1.1%).

Conclusion: WLWH attending PMTCT services had varied patterns of depressive symptoms, which were associated with stressors (recent diagnosis, food insecurity) and factors reflecting low social power (abuse, stigma, unintended pregnancy). Women experiencing concurrent abuse, stigma, and food insecurity should be prioritized for interventions to prevent persistent depression.

Keywords: Peripartum, depression, HIV, Kenya, trajectories, mental health

Introduction

Women living with HIV (WLWH) have increased likelihood of depression compared to women without HIV during pregnancy and postpartum.[62–64,191] Depression in pregnant WLWH may be related to fear of disclosure of their HIV status to their partner or transmission to their infant.[234] In addition, WLWH may experience challenges adhering to antiretroviral therapy (ART), adding further stress during the peripartum period. HIV-related stigma may compound psychosocial impacts of concurrent HIV-infection and new motherhood.[67] Consequences of peripartum depression among WLWH include HIV disease progression, HIV transmission to the infant, poor mother-infant attachment, and child socio-emotional developmental challenges.[81,86,87,235]

Few studies have longitudinally evaluated depressive symptoms among WLWH over pregnancy and the extended postpartum period. Most studies on peripartum depression among WLWH assess depressive symptoms at one point in time – either during pregnancy or postpartum.[62,63,191] Consequently, dynamic changes in depression over the pregnancy and postpartum period among WLWH are poorly characterized. Understanding patterns of depressive symptoms and what distinguishes WLWH at higher risk for persistent peripartum depression could inform prioritization of mental health services within PMTCT programs.

Trajectories of psychological health outcomes over time are increasingly utilized to illustrate courses of disease.[167,236] Group-based trajectory models provide a useful approach to identifying trajectories and have advanced our understanding of peripartum depression over the past decade.[57,166] Nearly all trajectory analyses for peripartum depression have been conducted in high-income settings.[57,166]

While some studies have modeled trajectories for peripartum depression among women in sub Saharan Africa (SSA), none have assessed trajectories in WLWH separately from HIV-negative women.[59,174–176] Prior studies in SSA identified a trajectory pattern describing persisting

depression throughout pregnancy and postpartum, as well as other groups with resolving symptoms or no depression.[59,174–176] These studies found stressful life events such as intimate partner violence, unintended pregnancy, and low socioeconomic status predicted higher-severity depressive symptom patterns.[59,174–176] Perinatal depressive symptom patterns may differ among WLWH compared to HIV-negative women, particularly as WLWH adjust to their diagnosis, learn their child's HIV status, disclose their HIV status, experience HIV stigma, and undergo virologic changes over time. Identifying patterns of peripartum depression among WLWH, and particularly predictors of persistent peripartum depression, could inform efficient mental health resource allocation within PMTCT programs.

We identified trajectories and cofactors of depression among WLWH during pregnancy and at multiple points postnatally through 24 months postpartum. Further, we identified predictors of persistent peripartum depression among WLWH.

Methods

Study design and participants

We conducted a longitudinal analysis nested in a randomized clinical trial (RCT) Mobile WAChX study (CT.gov NCT02400671). Study sites were located in Nairobi (Mathare and Riruta Health Centres) and Nyanza region (Ahero, Rachuonyo, Siaya and Bondo County Hospitals). The primary aim of the RCT was to compare the impact of 1-way SMS, 2-way SMS and control (no SMS) on antiretroviral therapy (ART) adherence, viral suppression, and retention in care among WLWH.[237]

Women attending antenatal care (ANC) within PMTCT programs at study clinics were screened and enrolled between November 2015 and May 2017. Eligibility criteria for the RCT included diagnosis of HIV, age ≥14 years, receiving MCH and HIV care at the study clinic, daily access to a mobile phone, and not participating in another research study. Overall, 825

participants provided consent and were enrolled into the study, 1 of whom was excluded due to duplicate enrollment.

Data collection procedure and measures

Surveys were administered at all study visits at enrollment; 6 weeks postpartum; and at 6, 12, 18, and 24 months postpartum using Open Data Kit on a tablet administered by study nurses in English. Surveys were translated into Kiswahili or Dholuo as needed. Surveys captured demographic characteristics, clinical data, and psychosocial factors, including depressive symptoms, HIV-related stigma, social support, and abuse by an intimate partner, close family member, or friend.

The Patient Health Questionnaire-9 (PHQ-9) screening scale was used to assess depressive symptoms at all study visits. Participants indicated the frequency of experiencing each of the 9 depressive symptom scale items over the last 2-weeks as: “not at all”, “several days”, “more than half the days”, or “nearly every day”. Item-level scores range from 0-3 where higher total scores describe higher severity of depressive symptoms (absolute range: 0-27).[147,238] Women were classified as having moderate-to-severe depressive symptoms (MSD) if the PHQ-9 score ≥10.[147,238]

Social support was assessed using the Medical Outcomes Study (MOS) scale at all study visits, where respondents report their confidence in being able to elicit support for various scenarios; higher scores indicate higher social support (range: 18-90). We evaluated HIV-related stigma with the 4-question version of the Stigma Scale for Chronic Illness (SSCI) among participants who were diagnosed with HIV prior to enrollment.[198] This scale includes items such as: “Because of my illness, some people avoided me”. If a participant endorsed any item on this scale, they were classified as experiencing stigma. Stigma was grouped into two sub-categories: 1) if they specifically endorsed feeling embarrassed or left-out they were classified as having

internalized stigma, 2) participants who felt they were being avoided or faulted for their HIV were classified as having *enacted* HIV-related stigma.

To evaluate experience of abuse, we administered the Abuse Assessment Screen to participants at enrollment.[239] We defined experiences of abuse "ever" or in the "last 12 months" as a response of "yes" to the question, "Have you been hit, slapped, kicked, or otherwise physically hurt by someone" "in the past year" or "ever"? To assess abuse during the postpartum period, we administered the same scale based on experience since the last study visit. Food insecurity was assessed using the 9-item Household Food Insecurity Access Scale (HFIAS) for prior 30-day food access, which has been validated in many contexts, including in Kenya.[240] We created 4-categories for food insecurity (food secure, mildly food insecure, moderately food insecure, and severely food insecure) according to the scale guide.[240] We abstracted clinical data from clinical patient files including plasma HIV viral load (VL) and ART initiation date. We categorized viral failure as having a VL ≥1000 copies/ml after being on ART for at least 4 months.

Statistical methods

The prevalence of MSD was calculated at every study visit. Correlates of MSD during the peripartum period were assessed using univariable and multivariable generalized estimating equation models (GEE) with a Poisson link and independent correlation structure, clustered by participant. Variables were included in the multivariable model if they were determined à priori to be associated with peripartum depression according to our conceptual model (Supplement Digital Content 1) and/or if they were associated with peripartum MSD at a significance level of alpha ≤0.1 in univariable analysis. Despite fitting model criteria, HIV-related stigma was not included in the multivariable model since a data collection error meant this information was not available for all WLWH. Covariates were specified as statistically significantly associated with peripartum MSD at p-value ≤0.05 in multivariable models. We evaluated potential multicollinearity between the two

abuse variables (“ever” or “last 12 months”), finding VIF of 1.07, which is considered no correlation.

To identify discrete trajectories of peripartum depressive symptoms, group-based trajectory models (GBTM) were performed among those attending the enrollment visit and at least one postpartum visit using the “traj” program in Stata.[241] This method groups individuals with similar patterns of an outcome measured over time to identify distinct trajectories.[54] The PHQ-9 continuous score measured repeatedly from pregnancy through 24 months postpartum was used to model patterns of depressive symptoms. Since the score range for the PHQ-9 is from 0-27, a censored normal distribution was used in modelling.

Group-based trajectory modelling utilizes a two-step process to identify the optimal number of discrete trajectory groups.[54] The initial step involves scrutinizing the Bayesian Information Criterion (BIC value), an indicator of model-fit, to evaluate the most optimal model (highest BIC value)[54] from a set of models with differing numbers of trajectories. The number of trajectory groups was hypothesized à priori to be between 1 and 5 based on considerations for clinical relevance. The functional form of all trajectories was initially fixed as cubic polynomials to determine the number of unique trajectories. Then the most statistically appropriate functional form of each trajectory (e.g., linear, quadratic, cubic) was identified based on observed plots and model BIC values. Changes in functional form were performed in a stepwise fashion to ensure each BIC comparison represented one change in model fit.

Adequacy of the final group-based trajectory model was assessed according to methods previously described.[167] Group-based trajectory models involve calculation of the “posterior probabilities of group membership” which are a set of probabilities that estimate a particular individual’s likelihood of belonging to each trajectory group based on that individual’s longitudinal depressive symptoms. The posterior probabilities are distinct from the “probability of group membership” which describes the proportion of the population that belongs to a trajectory group. Model adequacy can be evaluated by comparing the proportion of WLWH assigned to each group

to the sum of individual posterior probabilities of membership in each group. If differences between proportion assigned per group and sum of individual posterior probabilities was <5% we deemed the model was adequate. Further, we determined if the average posterior probability of membership in each group among the individuals assigned to that group was at least 80%.[167]

GBTM-extension methods can accommodate nonrandom attrition in the study population over time by allowing differential missingness across trajectory groups, thus relaxing the assumption of missingness completely at random.[167,171] In our sample, 94% of WLWH had pregnancy and postpartum PHQ-9 scores, yet only 32% attended all 6 study visits (sessions attended Median, Interquartile range [IQR]: 4 [3-6]). Thus, nonrandom attrition was accounted for in our model.[167,171] Facility was included as a baseline predictor of group membership since median PHQ-9 scores varied by facility; this inclusion improved BIC.

We identified predictors of trajectory group membership using multinomial logistic regression. Differences in characteristics of WLWH with persistent depression throughout the peripartum period were compared using t-tests (continuous predictors) and Fisher's exact tests (categorical predictors). Analyses were conducted using Stata version 15.

Results

Among 824 WLWH enrolled in the study, the median age was 28 years (IQR: 23-30), median gravidity was 3 IQR: 2-4), and nearly half (369, 45%) had unintended pregnancies (Table 5b.1). Most women (84%) were married or cohabiting, and over three quarters (77%) reported completion of at least primary education. The median time since HIV diagnosis was 2 years (IQR: 0.1-5.0), most participants (82%) disclosed their HIV status to someone and 87 women (11%) reported abuse in the year prior to enrollment.

Prevalence of moderate-to-severe depressive symptoms in the peripartum period

During pregnancy, 8.6% of WLWH had MSD, with a median PHQ-9 score of 2 (IQR: 0-5) (Figure 5b.1). A median PHQ-9 score of 1 (IQR: 0-4) was recorded at postpartum visits of 6 weeks, 6 months, and 12 months, while lower median scores of 0 (IQR: 0-3) were recorded at 18

and 24 months postpartum. Among those attending at least 1 postpartum visit, 9.0% (70/776) reported any postpartum MSD. Across the peripartum period, 14.6% (120/824) of WLWH had MSD at some point. Cronbach's alpha for the PHQ-9 was 84.6%. Cronbach's alpha for the social support scale was 95.9%, 94.2% for HFIAS, and 72.1% for the stigma scale.

Predictors of peripartum moderate-to-severe depressive symptoms

In univariable analysis, the risk of ever experiencing any MSD during pregnancy or postpartum was substantially higher among those experiencing abuse by someone close to them (an intimate partner or family/friend) before enrollment (RR: 2.7, 95% CI: 1.8-4.9). Risk of MSD increased with more recent abuse with a 3.8-fold increased risk among women who experienced abuse in the 3 months prior to the postpartum study visit or 12 months before the pregnancy visit (RR: 3.8, 95% CI: 2.6-5.4) (Table 5b.1). Women with severe food insecurity had a 2.7-fold higher risk of MSD (95% CI: 1.9-3.8). If a women's pregnancy was unintended, risk of MSD was 60% higher (RR: 1.6, 95% CI: 1.1-2.3) than those reporting intended pregnancies. WLWH who reported more support from their social networks had lower risk of peripartum MSD (RR: 0.97, 95% CI: 0.96-0.98). Risk of MSD fluctuated over pregnancy and postpartum. MSD risk was 3-times higher during pregnancy than between 12-24 months postpartum (RR: 3.14, 95% CI: 2.09-4.69). Risk of MSD was also higher within 6-12 months postpartum than after 12 months postpartum (RR: 1.8, 95% CI: 1.1-2.8). Frequency of any peripartum MSD differed significantly by facility (range: 4.3%-44.2%).

Characteristics related to HIV predicted MSD. WLWH who reported HIV-related stigma had over 4-times higher risk for peripartum MSD than those not reporting stigma (RR: 4.4, 95% CI: 3.1-6.3). WLWH who learned of their HIV diagnosis within the prior two years (RR: 1.8, 95% CI: 1.2-2.6) were also more prone to MSD than those with diagnoses >2 years. Risk of MSD was lower among WLWH who disclosed their HIV status to others (RR: 0.4, 95% CI: 0.2-0.8) compared to WLWH who did not disclose. Among WLWH on ART for $\geq$ 4 months (n=474), viral failure (VL

>1000 c/ml) was associated with over twice the risk of peripartum MSD (RR: 2.48, 95% CI: 1.22-5.07).

MSD was not associated with age, marital status, monthly household income, household overcrowding, or completion of primary education. Risk for subsequent postpartum MSD was similar among women who suffered loss of an infant during follow-up and women with infants who lived through follow-up (RR: 0.8, 95% CI: 0.3-2.3, p=0.739) (54/824 [6.55%] of WLWH experienced infant loss, 83/2603 [3.2%] of postpartum visits had a prior infant loss reported). Risk of any peripartum MSD did not differ by mHealth randomization arm (p=0.904), thus we did not include SMS intervention group as a factor in multivariable analysis.

In multivariate analyses, abuse ever before enrollment or since the prior visit remained associated with peripartum MSD after adjustment for confounders (Ever: adjusted RR [aRR]: 1.7, 95% CI: 1.2-2.5; Since prior visit: aRR: 1.6, 95% CI: 1.1-2.3), as did experiencing severe food insecurity (aRR: 2.2, 95% CI: 1.5-3.0). Higher social support also remained significantly associated with lower MSD (aRR: 0.99, 95% CI: 0.98-0.99), while HIV disclosure was no longer significantly associated with MSD. The temporal differences in risk of MSD remained, with highest risk during pregnancy, followed by 6-12 months postpartum, compared to 12-24 months postpartum.

Peripartum depressive symptom trajectories

A four-trajectory model corresponded with the highest BIC value (Supplemental Digital Content 2) and was selected to present discrete patterns of depressive symptoms among WLWH who attended enrollment and at least 1 postpartum visit (Figure 5b.2). One depressive symptom group described women with MSD persisting during pregnancy and postpartum (“persistent MSD”, 8/776, 1.1%). The other three trajectories showed patterns consistently below moderate depressive symptoms: symptoms resolve over time (“mild resolved”, 100/776, 12.6%), symptoms increasing in postpartum yet remained low (“increase postpartum”, 368/776, 47.9%), consistent

low symptoms (“consistent low”, 300/776, 38.5%). Functional forms of these trajectories were quadratic (Figure 5b.2).

The proportion of WLWH in each depressive symptom group aligned well (within 0.5%) with the proportion expected in each group based on the sum of posterior probabilities, supporting model adequacy (Supplemental Digital Content 3). Further, the average posterior probability of belonging to a depressive symptom group among individuals assigned to each group exceeded our pre-specified threshold of >80% for each depressive symptom group (absolute range: 81.8%-97.9%).

Predictors of depressive symptom trajectories

We identified predictors of group membership in the “persistent MSD”, “Mild resolved”, and “Increase postpartum” groups compared to the “Consistent low” group. Persistent MSD was substantially and statistically significantly associated with abuse by a partner (Relative risk ratio [RRR]: 12.6, 95% CI: 2.9-53.9) compared to consistent low depressive symptoms (Table 5b.2). Since only 8 women had persistent MSD, we had low power to detect other differences. Women experiencing household crowding were more likely to have increased depressive symptoms postpartum, than consistent low depressive symptoms (RRR: 2.3, 95% CI: 1.6-3.1). Higher education level, pregnancy intention, higher social support score, and not experiencing food insecurity were also associated with membership in the “increase postpartum” group compared to consistent low. Members of the “mild resolved” group had lower social support scores than those in the “consistent low” group.

Cofactors of persistent peripartum moderate-to-severe depressive symptoms

Eight women with “persistent MSD” during the peripartum period had a high prevalence of psychological stressors during pregnancy compared to other depressive symptom groups with non-persistent MSD. Stressors included abuse, severe food insecurity, and HIV-related stigma (Table 5b.3).

Sensitivity analysis

In sensitivity analyses, we evaluated cofactors of developing postpartum MSD among the subgroup of WLWH who did not have MSD in pregnancy; our findings were robust (data not shown). We compared WLWH attending all visits to those who missed at least one visit, finding higher prevalence of MSD in pregnancy among those with imperfect attendance. Prior to performing GBTM, we hypothesized that WLWH may follow four distinct trajectories characterized by having MSD throughout pregnancy and postpartum, having MSD in pregnancy only, MSD in postpartum only, or never having MSD. We manually formed these groups and plotted their average PHQ-9 scores over time (data not shown). Prevalence and patterns within pre-specified groups were similar to the GBTM results.

Discussion

In this longitudinal evaluation of depressive symptoms among WLWH serially assessed from pregnancy through 24 months postpartum, we found substantial prevalence of ever having MSD during pregnancy and postpartum. We found a higher prevalence of MSD in pregnancy than postpartum and 4 discrete depression symptom groups: 3 including low/mild symptoms that sometimes resolved (consistently low: 38.5%, mild resolved: 12.6%, increase postpartum: 47.9%) and 1 of which identified a profile of WLWH with persistent depression from pregnancy through 24 months postpartum (1.1%). Cofactors for MSD during pregnancy and postpartum included stressors such as recent HIV diagnosis, unintended pregnancy, food insecurity, and non-disclosure. In addition, stressors reflected low social power of women (stigma, low social support, and abuse). This is the first study to identify trajectories of peripartum depression among a cohort of WLWH in sub-Saharan Africa. Our results contribute new understanding about patterns and cofactors for peripartum depression which could inform timing and prioritization of mental health services integrated within routine PMTCT services.

Our finding that 14.6% of WLWH experienced depression at least once during the perinatal period was consistent with global estimates from pooled analysis among low- and middle-income countries (13.1%)[78] We identified predictors of peripartum depression which

echoed findings from a recent systematic review and meta-analysis among African women, particularly that experience of abuse from an intimate partner and low social support were substantial risk factors.[70] While we did not find lower household income as a risk factor for peripartum depression,[70] women facing severe food insecurity – another marker of low socioeconomic status – was associated with peripartum depression. Women reporting HIV-related stigma were much more likely to report peripartum depression, as in other studies.[213,223,224] Those who experienced virologic failure during pregnancy, despite engagement in a PMTCT program for at least 4 months, were twice as likely to report peripartum depression.[242] We did not find a relationship between infant death and later postpartum depression;[70] however we may have lacked power to detect this association. In a separate analysis, our team found an association between mild-to-severe depressive symptoms during pregnancy and stillbirth in this cohort.[243]

In trajectory analysis, we identified a small group (1.1%) with MSD that persisted from pregnancy through two years postpartum. Prior peripartum trajectory analyses in SSA similarly identified a group with persistent depression (3.1%-8.6%).[59,174–176] However these analyses defined the "persistent depression" group differently and most of the analyses utilized the Edinburgh Postnatal Depression Scale (EPDS) instead of the PHQ-9.[59,174–176] Across studies, persistent MSD has been noted to be uncommon (<9%), indicating that a small, yet vulnerable group may particularly benefit from mental health services during antenatal and postnatal care. The two most frequent groups in our sample of WLWH were a group that experienced low depressive symptoms which increased slightly (but remained low) in the postpartum period (47.9%), and a group with consistently low depressive symptoms (38.5%). Other studies similarly identified the most prevalent group as one with consistently low symptoms.[59,60,174,176] These women could be ruled out as not requiring additional monitoring and referral for mental health treatment.

The other depressive symptom group showed mild severity of depressive symptoms during pregnancy which resolved over time. While frequency of persistent MSD was low, many

more WLWH (about 15%) experienced at least one episode of peripartum MSD highlighting that some individuals in the “mild resolved”, “increase postpartum”, and “consistent low” groups experienced episodic MSD. However, the average trajectory patterns among the depressive symptom groups remained below clinical significance for referral to mental health services throughout the peripartum period. This suggests that >90% of WLWH may either self-resolve episodes of MSD or never experience peripartum MSD. Frequent depressive symptom screening may over-estimate the prevalence of peripartum depression requiring high-intensity formal treatment (e.g., antidepressant medication) since women whose mental health issues would spontaneously resolve before clinical detection are included in more frequent prevalence estimates.[96,244] However these women may still benefit from lower-intensity psychological intervention (e.g., peer support, problem-solving therapy) to prevent consequences of episodic depression on quality of life, relationships, and parenting.

Women with persistent MSD experienced acute and concurrent stressors during pregnancy (abuse, severe food insecurity, and HIV-related stigma). Careful psychosocial evaluation to identify women with multiple co-occurring stressors during pregnancy may distinguish those with persistent versus spontaneously-resolving peripartum depressive episodes. This approach may represent a more efficient use of health system resources compared to more frequent depression screening in the absence of comprehensive psychosocial evaluation within PMTCT.

Several limitations should be considered when interpreting our study findings. There was inconsistent attendance across six study visits over the follow-up period. However, overall retention through 24 months retention was high (89%). Episodic attrition may have introduced selection bias if participants with higher depressive symptoms were systematically less likely to attend follow-up visits. In sensitivity analysis we found those with imperfect attendance had higher prevalence of MSD in pregnancy compared to those who attended all visits; thus our estimates may underestimate the frequency of postnatal depression and the proportion of women with

persistent peripartum MSD. Group-based trajectory models accounted for nonrandom attrition; thus, we were able to mitigate the impact of attrition on GBTM-based estimates. We did not collect information about antidepressant use. Antidepressant medications are included in the Kenya Essential Package for Health[245], however depression screening is not currently a standard of care in Kenyan PMTCT[246], thus we anticipate no study participants were currently taking antidepressants.

We did not account for time-varying factors within GBTM since models including time-varying variables did not converge. Our results are comparable to the previous peripartum depression trajectory analyses in SSA which also chose not to include time-varying predictors within model specification.[59,174–176]

Conclusions

In summary, we found four patterns of depressive symptoms experienced by WLWH in Kenya. Overall, 14.6% of the WLWH had MSD at some point during repeated screening from pregnancy through 24 months postpartum. The majority (>90%) of WLWH spontaneously resolved or never had peripartum MSD. A small group with comorbid, high-impact stressors experienced depression that persisted from pregnancy through late postpartum. Interventions to address depressive symptoms should be integrated into PMTCT programs and prioritized for those with overlapping experiences of abuse by a close loved one, HIV-related stigma, and/or financial stress impacting food security. Psychological treatment methods such as cognitive behavioral therapy, interpersonal therapy, and problem-solving counseling have been shown to be effectively delivered by lay or peer counselors in low-resource settings[94,178,247] and could be offered to WLWH at risk for persisting depression during PMTCT care. Resources should address social determinants of health such as food justice, preventing stigma, and reducing violence against women to holistically impact perinatal depression.

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TABLES AND FIGURES

Table 5b.1. Longitudinal predictors of moderate-to-severe depressive symptoms from pregnancy to 24 months postpartum among Kenyan WLWH (3426 observations from 824 participants)

	MSD in peripartum		No MSD in peripartum		Univariable Analysis[1]			Multivariable Analysis[2]		
	N	n or median (% or IQR)	N	n or median (% or IQR)	RR	95% CI	p-value	aRR	95% CI	p-value
Baseline factors										
Age (years)	120	27.5 (23-30)	704	27 (23-31)	0.97	(0.94-1.01)	0.136			
Adolescent or young woman (<25 years)	120	44 (36.7)	704	243 (34.5)	1.10	(0.75-1.62)	0.618			
Primary education completed	120	84 (70.0)	704	549 (78.0)	1.10	(0.75-1.62)	0.618			
Married/cohabiting	120	94 (79.0)	704	600 (85.2)	0.75	(0.48-1.17)	0.203			
Monthly household income (USD)	71	60 (30-120)	456	80 (40-150)	1.00	(0.99-1.00)	0.708			
Household crowding (≥3/room)	120	37 (30.8)	704	253 (35.9)	0.85	(0.56-1.29)	0.450			
Gravidity	120	3 (2-4)	704	3 (2-4)	0.97	(0.84-1.13)	0.755			
Unintended pregnancy	120	65 (54.2)	704	304 (43.4)	**1.57**	**(1.07-2.31)**	**0.020**	1.33	(0.94-1.89)	0.102
HIV diagnosis within 2 years (vs. ≥2)	120	42 (60.0)	700	309 (44.0)	**1.75**	**(1.17-2.62)**	**0.007**	**1.49**	**(1.02-2.18)**	**0.036**
VL >1000 c/ml ≥4 months since ART start	56	14 (25.0)	418	46 (11.0)	**2.48**	**(1.22-5.07)**	**0.012**			
Abused by partner or relative/friend (ever)	120	40 (33.3)	704	111 (15.8)	**2.71**	**(1.81-4.06)**	**<0.001**	**1.73**	**(1.19-2.53)**	**0.004**
SMS group	120		704							
One way vs. Control		38 (31.7)		232 (33.0)	0.97	(0.61-1.56)	0.907			
Two way vs. Control		42 (35.0)		235 (33.4)	1.23	(0.77-1.96)	0.381			
Time-varying factors										
HIV status disclosed to other(s)*	113	85 (75.2)	691	575 (83.2)	**0.34**	**(0.20-0.56)**	**<0.001**	0.74	(0.48-1.14)	0.174
HIV-related stigma*	78	48 (61.5)	373	135 (36.2)	**4.39**	**(3.08-6.26)**	**<0.001**			
Internalized HIV-related stigma	78	45 (57.7)	377	122 (32.7)	**4.54**	**(3.21-6.42)**	**<0.001**			
Enacted HIV-related stigma	78	16 (20.5)	377	44 (11.8)	**2.39**	**(1.62-3.53)**	**<0.001**			
Abused by partner or relative/friend*	120	29 (24.2)	704	63 (8.9)	**3.78**	**(2.64-5.41)**	**<0.001**	**1.60**	**(1.11-2.30)**	**0.012**
Social support score*	120	58.5 (42-70.5)	704	64 (51-72)	**0.97**	**(0.96-0.98)**	**<0.001**	**0.99**	**(0.98-0.99)**	**0.038**
Severe food insecurity*	118	50 (42.4)	692	183 (26.4)	**2.72**	**(1.96-3.76)**	**<0.001**	**2.17**	**(1.54-3.04)**	**<0.001**
Time since delivery (days)**					0.99	(0.99-1.00)	0.101			
Pregnancy vs. >12 months pp					**3.14**	**(2.09-4.69)**	**<0.001**	**3.14**	**(1.96-5.03)**	**<0.001**
≤6 months pp vs. >12 months pp					1.38	(0.89-2.15)	0.153	1.40	(0.86-2.28)	0.180
6-12 months pp vs. >12 months pp					**1.77**	**(1.13-2.79)**	**0.014**	**1.68**	**(1.01-2.77)**	**0.044**

Moderate-to-severe depressive symptoms (MSD), Postpartum (pp), Antiretroviral Therapy (ART), Viral load (VL), Short message service (SMS)

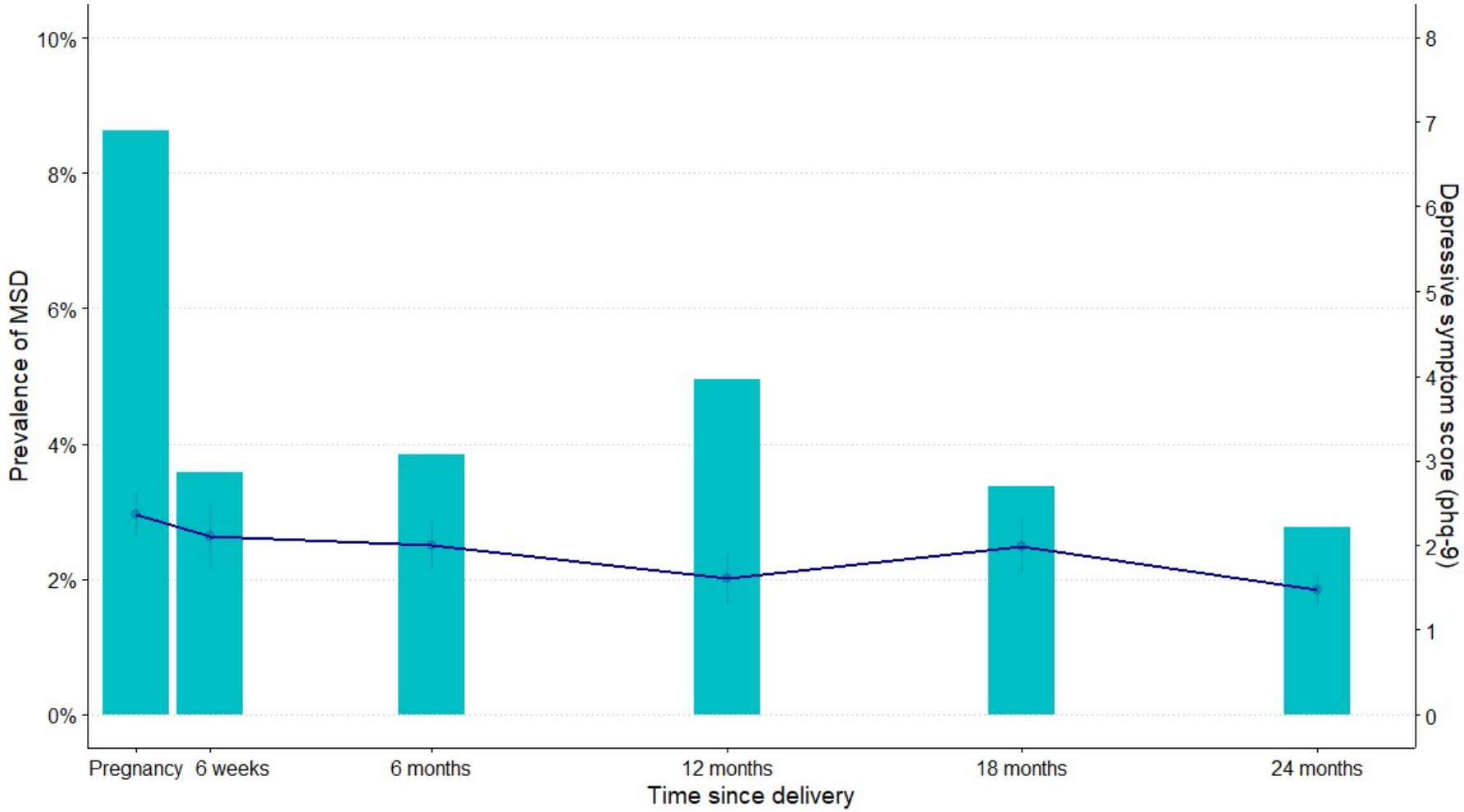
* During/before pregnancy (for enrollment visit) or since prior visit (for postpartum visits); N(%) reported for enrollment visit

** N(%) not reported since this variable describes timing in peripartum stage which is not a baseline variable

[1] GEE model clustered by patient; effect sizes for continuous variables model per unit increase in risk

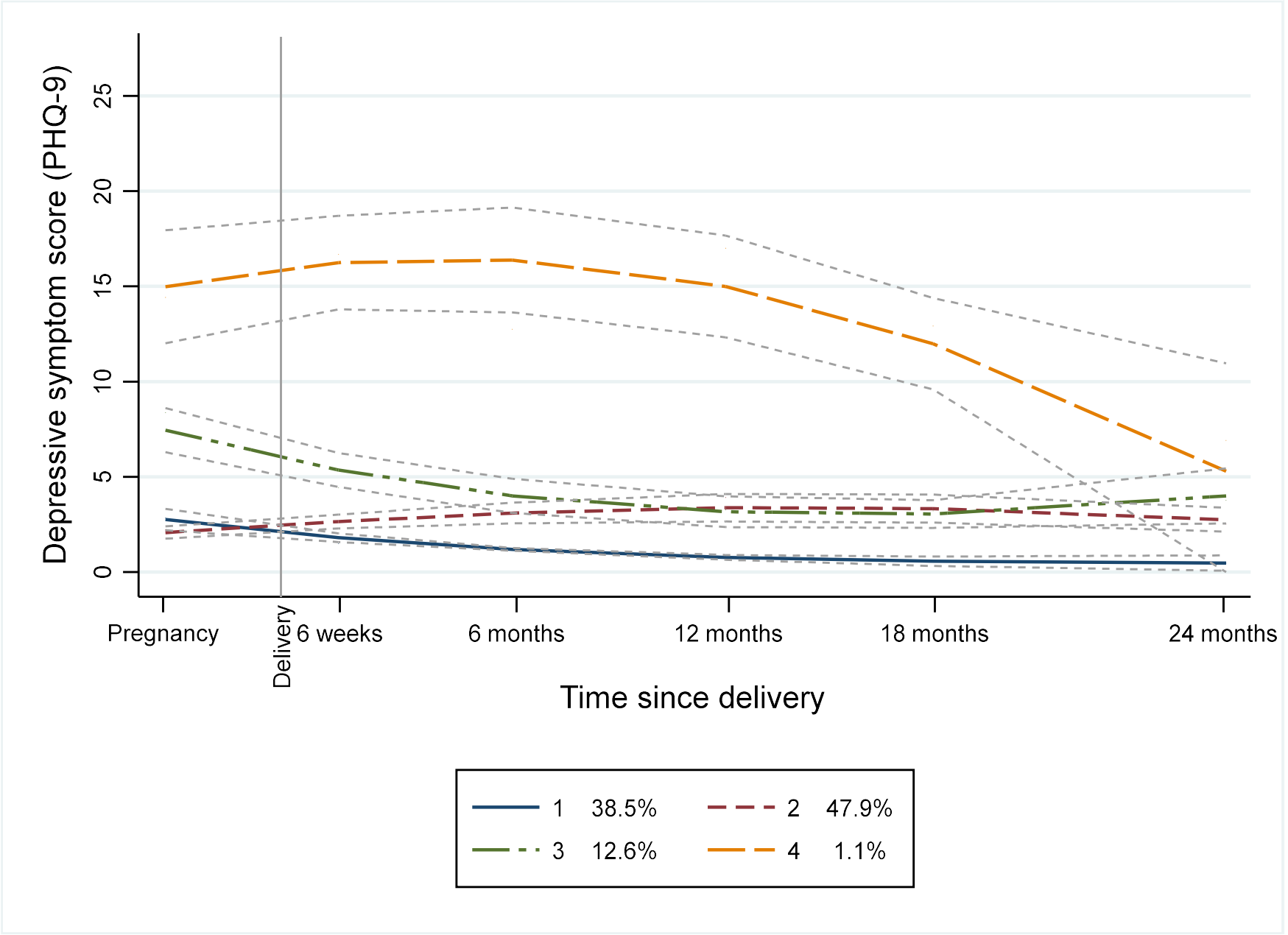
[2] GEE model clustered by patient, adjusted for facility, unintended pregnancy, HIV diagnosis within 2 years, abused by a partner or relative/friend (ever), HIV status disclosure (time-varying), abused by partner or relative/friend (time-varying), social support score (time-varying), severe food insecurity (time-varying), time since delivery; effect sizes for continuous variables model per unit increase in risk

Figure 5b.1. Frequency of moderate-to-severe depressive symptoms and mean PHQ-9 score by study visit



Pregnancy			6 weeks PNC			6 months PNC			12 months PNC			18 months PNC			24 months PNC		
N	PHQ-9 score Median (IQR)	MSD N (%)	N	PHQ-9 score Median (IQR)	MSD N (%)	N	PHQ-9 score Median (IQR)	MSD N (%)	N	PHQ-9 score Median (IQR)	MSD N (%)	N	PHQ-9 score Median (IQR)	MSD N (%)	N	PHQ-9 score Median (IQR)	MSD N (%)
	2 (0-5)	71 (8.6)	595	1 (0-4)	24 (4.1)	487	1 (0-4)	17 (3.5)	431	1 (0-4)	21 (4.9)	356	0 (0-3)	10 (2.8)	735	0 (0-3)	20 (2.7)

Figure 5b.2. Trajectories of peripartum depressive symptoms from pregnancy through 24 months postpartum among Kenyan WLWH (n=776)



Patient health questionnaire-9 (PHQ-9), Moderate-to-severe depressive symptoms (MSD)

Table 5b.2. Predictors of peripartum depressive symptom trajectory group membership: results from multinomial logistic regression

	Group 2 vs Group 1 Increase postpartum vs. Consistent low n=368		Group 3 vs Group 1 Mild resolved vs. Consistent low n=100		Group 4 vs Group 1 Persistent MSD vs. Consistent low n=8	
Baseline characteristics	**Relative risk ratio (RRR)**	**95% CI**	**RRR**	**95% CI**	**RRR**	**95% CI**
Adolescent or young woman (<25 years)	0.92	0.66-1.27	1.28	0.80-2.04	1.20	0.28-5.12
Primary education completed	**0.61**	**0.42-0.88**	1.42	0.87-2.30	**	**
Married/cohabiting	0.91	0.59-1.39	0.84	0.45-1.58	1.14	0.14-9.49
Household crowding (≥3/room)	**2.27**	**1.64-3.14**	0.49	0.28-0.89	0.87	0.17-4.40
Unintended pregnancy	**0.65**	**0.48-0.89**	1.34	0.85-2.11	1.76	0.41-7.49
HIV diagnosis within 2 years (<2 vs. ≥2 years)	1.02	0.75-1.39	1.25	0.79-1.96	1.25	0.31-5.08
HIV status disclosed to partner	0.85	0.59-1.23	0.99	0.57-1.73	0.29	0.07-1.20
HIV-related stigma	1.39	0.89-2.16	1.59	0.91-2.80	**	**
Abused by partner or relative/friend (within last year)	1.24	0.71-2.18	1.89	0.91-3.91	**12.64**	**2.96-53.99**
Social support score	**1.04**	**1.02-1.05**	**0.98**	**0.97-0.99**	0.99	0.95-1.03
Severe food insecurity	**0.42**	**0.29-0.61**	1.20	0.75-1.91	3.01	0.71-12.88
SMS group						
One way vs. Control	1.01	0.69-1.47	1.07	0.62-1.85	1.04	0.14-7.53
Two way vs. Control	0.99	0.68-1.44	0.90	0.52-1.58	1.98	0.35-11.05

Bolding denotes statistical significance (p-value<0.05)
**Sample size in group 4 is too small for stable estimate

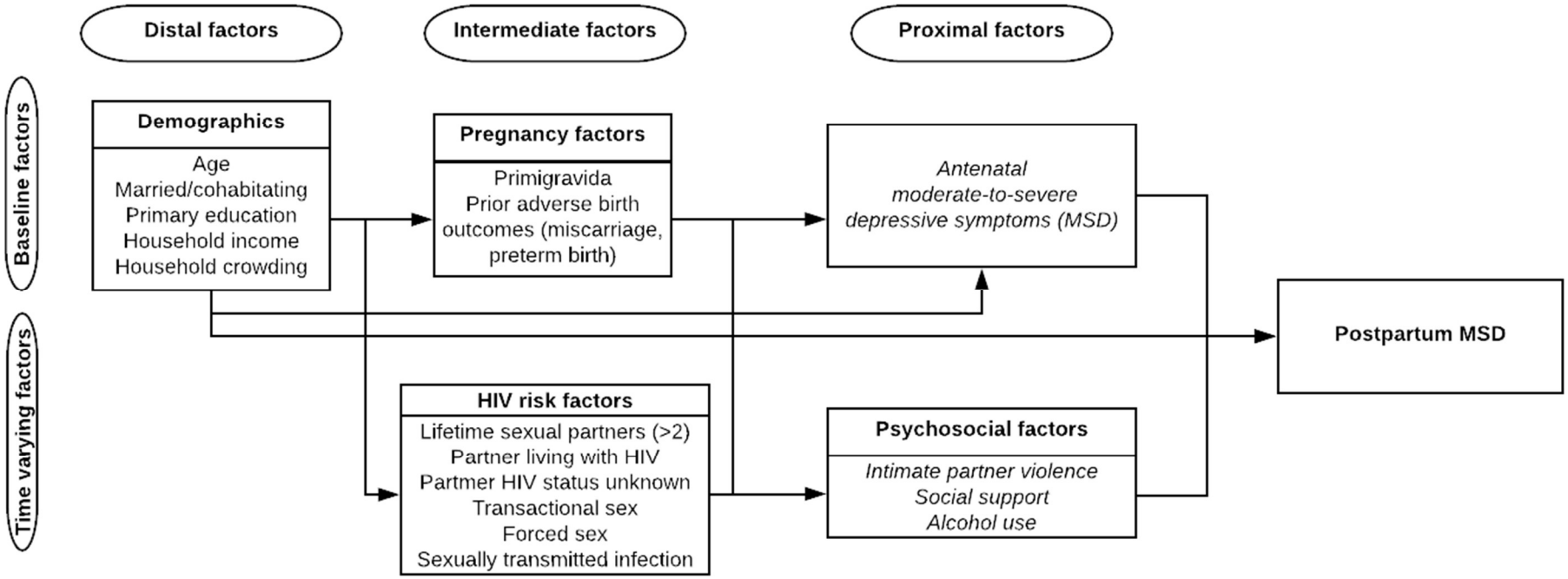
Table 5b.3. Predictors of persistent peripartum moderate-to-severe depressive symptoms (n=776)

	Persistent peripartum MSD trajectory n=8 (1.1%)	**Non-persistent/No MSD trajectories** ("increase postpartum", "Mild resolved", "Consistent low") n=816 (98.9%)	
Baseline Characteristics	**n (%) or median (IQR)**	**n (%) or median (IQR)**	**p-value**
Age (years)	26.5 (23.5, 29.0)	27.0 (23.0, 31.0)	0.60
Adolescent or young woman (<25 years)	3 (37.5%)	255 (33.2%)	0.73
Primary education completed	8 (100.0%)	587 (76.4%)	0.60
Married/cohabiting	7 (87.5%)	653 (85.1%)	1.00
Household crowding (≥3/room)	2 (25.0%)	270 (35.2%)	0.72
Unintended pregnancy	5 (62.5%)	341 (44.6%)	0.48
HIV diagnosis within 2 years (<2 vs. ≥2 years)	4 (50.0%)	347 (45.4%)	1.00
HIV status disclosed to other(s)	5 (62.5%)	626 (83.4%)	0.14
HIV-related stigma	6 (100.0%)	162 (38.8%)	**0.004**
Abused by partner or relative/friend (within last year)	4 (50.0%)	83 (10.8%)	**0.007**
Social support score	57.5 (50.5, 66.0)	64.0 (50.0, 72.0)	0.49
Severe food insecurity	5 (62.5%)	213 (28.2%)	**0.047**
SMS group (control)	2 (25.0%)	259 (33.7%)	0.74
One way	2 (25.0%)	252 (32.8%)	
Two way	4 (50.0%)	257 (33.5%)	

Moderate-to-severe depressive symptoms (MSD), Short message service (SMS)
P-values from Fisher's exact tests

APPENDIX

Supplemental Digital Content 1. Conceptual model for perinatal depressive symptoms and cofactors



Supplement Digital Content 2. Model selection process for selected group-based trajectory model for Kenyan women living with HIV

	Bayesian Information Criterion (BIC)	Akaike Information Criterion (AIC)	Log Likelihood (LL)
Step 1: Identifying number of trajectory groups by best-fit model[1]			
One trajectory group			
Two trajectory groups	-7188.5	-7169.9	-7161.9
Three trajectory groups	-7107.1	-7069.8	-7053.8
Four trajectory groups[2]	-7097.2	-7041.4	-7010.4
Five trajectory groups	-7110.2	-7017.1	-6977.1
Step 2: Identifying polynomial form of each trajectory group by best-fit model[2]			
Model selected based on BIC value: Group 1 ("Consistent low"): quadratic Group 2: ("Mild resolved") quadratic Group 3: ("Increase postpartum") quadratic Group 4: ("Persistent MSD") quadratic	-7084.7	-7021.8	-6994.8
Model selected based on BIC value: Group 1 ("Consistent low"): quadratic Group 2: ("Mild resolved") quadratic Group 3: ("Increase postpartum") quadratic Group 4: ("Persistent MSD") quadratic ***Facility included as baseline predictor[3]***	-6995.3	-6925.5	-6895.5

[1]We compared BIC for each of the four models in Step 1 and selected the 5-trajectory model since it had the most optimal BIC value. All trajectory groups were initially modeled using cubic polynomials. We used the extension for non-random attrition to relax assumptions of missingness completely at random.

[2]We ran all model permutations for 4-trajectories with polynomial forms (linear – quadratic) and selected the best fitting model using BIC. We used the extension for non-random attrition to relax assumptions of missingness completely at random.

[3]We included facility as a baseline predictor of group membership to account for variation in MSD by facility. Inclusion improved BIC

Supplemental Digital Content 3. Model adequacy characteristics for selected group-based trajectory model for Kenyan women living with HIV

	Group 1: "Consistent low" n=300	**Group 2: "Mild resolved"** n=100	**Group 3: "Increase postpartum"** n=368	**Group 4: "Persistent MSD"** n=8
Proportion in each group based on assignments for maximum posterior probability[1]	38.7%	12.9%	47.4%	1.0%
Expected proportion in each group based on sums of posterior probabilities[1]	38.5%	12.6%	47.9%	1.1%
Average posterior probabilities[2]	81.8%	74.3%	87.0%	97.9%

[1]We achieved model adequacy since the proportion based on maximum posterior probability and expected proportion based on sums of posterior probabilities are within <5% of each other.
[2]We achieved model adequacy since average posterior probability in each group was ≥70%

Chapter 6: Maternal depressive symptoms increase risk for pregnancy loss, preterm birth, and low birthweight among Kenyan mother-infant pairs

Submitted for peer-reviewed publication at the time of dissertation completion

Maternal depressive symptoms increase risk for pregnancy loss, preterm birth, and low birthweight among Kenyan mother-infant pairs: a prospective cohort study

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Keywords: Depression, pregnancy, sub-Saharan Africa, social support, intimate partner violence, perinatal outcomes, pregnancy loss, low birthweight

Abstract

Background: Evidence gaps remain regarding the influence of prenatal psychosocial factors on adverse pregnancy outcomes. We evaluated relationships between psychosocial factors and perinatal outcomes among Kenyan women.

Methods: We analyzed data from a prospective study enrolling HIV-negative women in pregnancy (NCT03070600) in 20 antenatal clinics in Western Kenya. Study nurses assessed depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CESD-10), social support using the Medical Outcomes Survey scale (MOS-SSS), IPV with the Hurt, Insult, Threaten, Scream scale (HITS), and pregnancy outcomes at 6-weeks postpartum. Cox proportional hazards and Poisson regression models were used to evaluate relationships between depressive symptoms (moderate-to-severe [MSD, CESD-10 $\geq$10] and mild-to-severe [Mild-SD, CESD-10 $\geq$5]), low social support (MOS-SSS <72), and IPV (HITS $\geq$10) with pregnancy loss, stillbirth, preterm birth (PTB), neonatal mortality, and low birthweight (LBW).

Findings: Among 4153 women, median age was 24.0 years, 24% (994/4153) had MSD, 55% (2273/4153) mild-SD, 37% (1547/4151) low social support, and 8% (323/4153) experienced IPV. Pregnancy loss was 5-fold higher among women with MSD (Adjusted Hazard Ratio [aHR]:5.0, 95% CI: 2.4-10.4, <0.001); 37% of losses were attributable to MSD. Mild-SD was associated with PTB (aHR:1.4, 95% CI:1.0-1.9, p=0.034), and LBW (Adjusted Relative Risk [aRR]:1.9, 95% CI:1.2-3.0, p=0.006). Stillbirth risk was doubled among women reporting low social support (aHR: 2.4, 95% CI: 1.1-4.9, p=0.021).

Interpretation: Adverse perinatal outcomes were common in this multi-site cohort and associated with prenatal depressive symptoms and low social support. Integrating mental health services within MCH systems may improve perinatal outcomes.

Funding: National Institutes of Health

What is already known on this topic:

- Depression in pregnancy is common and associated with adverse perinatal outcomes of preterm birth (PTB), low birthweight (LBW), and infant death
- Yet these relationships are understudied in sub-Saharan Africa—the region with the highest burden of adverse perinatal outcomes.

What this study adds:

- We evaluate potential relationships between multiple psychosocial factors (depression, low social support, intimate partner violence) and multiple adverse perinatal outcomes of pregnancy loss, stillbirth, PTB, LBW, small-for-gestational age, and neonatal death among a large cohort of Kenyan women.
- This is the largest study to assess maternal mental health and >3 birth outcomes among African mother-infant pairs.

How this study might affect research, practice or policy:

- Our findings that maternal depressive symptoms increase risk of pregnancy loss, PTB, and LBW, and that lack of social support increased risk of stillbirth, highlight the need for integrated mental health services within maternal child health settings to improve dyadic outcomes.
- Implementation science strategies should evaluate approaches to integrating depression screening within MCH visit schedules, and to assess potential on-site depression interventions, and monitoring or referral strategies to ultimately improve maternal and child health and well-being.

Introduction

Over 10% of pregnant women experience depression; the burden is higher in low- and middle-income countries (LMICs), particularly in sub-Saharan Africa (SSA) where a quarter of childbearing women are depressed.[162] Changes in reproductive hormones during gestation and innate genetic factors are compounded by stressors, such as inadequate social support and violence by an intimate partner, to impact mental distress during this period.[13,81,84] Maternal mental distress during pregnancy influences a range of adverse maternal and child health outcomes.[81] A meta-analysis utilizing data from high-income countries (HICs) and LMICs found an association between depression during pregnancy with both preterm birth (PTB) and low birthweight (LBW).[33] Subsequent meta-analyses confirmed these relationships,[32,248] additionally identifying maternal depressive symptoms as a predictor of small-for-gestational age[248,249], and infant death.[250] Efforts to improve mental health and psychosocial support among pregnant women may lead to dyadic health gains.

Promotion of routine maternal child health (MCH) care has improved maternal and child health globally,[251] but there is still need to improve neonatal survival,.[252] ,[253,254] particularly in Africa, where 43% of global neonatal deaths occur.[255] Adverse perinatal outcomes, including pregnancy loss, stillbirth, preterm birth, low birthweight, and small-for-gestational age occur more frequently in LMICs and contribute to suboptimal neonatal outcomes.[256,257]

The high prevalence of maternal depression in SSA (25%)[19,162], combined with slower gains in neonatal health, make understanding the potential linkages between maternal mental health and perinatal outcomes vital in this region. Routine MCH services are well-attended in SSA (>95%),[140] offering a high-impact setting for preventing and treating depression in pregnancy for dyadic benefit.[91] Few studies focus on linked maternal mental health and infant outcomes in this region. A recent meta-analysis identified only 3 studies in SSA (Ethiopia[258], Ghana and Cote D'Ivoire[259], and Kenya[260]) evaluating antenatal depression and birth outcomes.[261] Pooled results (n=1511 participants) indicated increased risk of PTB and LBW with maternal depression in

pregnancy.[261] These studies had relatively small sample sizes and evaluated few birth outcomes, limiting their scope. To our knowledge, no studies among African mother-infant pairs have evaluated the impact of antenatal depression on >3 adverse birth outcomes from pregnancy through post-delivery.

We evaluated relationships between psychosocial factors during pregnancy (depression, low social support, intimate partner violence) and adverse perinatal outcomes of pregnancy loss, stillbirth, preterm birth, low birthweight, small-for-gestational age, and neonatal mortality among perinatal women in Kenya.

Methods

Study design and participants

This analysis was nested in the PrEP implementation for Mothers in Antenatal Care study (PrIMA) which was a cluster randomized trial comparing two models for pre-exposure prophylaxis implementation among pregnant women in Western Kenya (NCT03070600).[168] Women attending antenatal care (ANC) between Jan 15, 2018, and July 31, 2019 in 20 MCH clinics were screened and enrolled. Eligible women were pregnant, HIV-uninfected, ≥15 years old and were able to provide consent.

Procedures

Study nurses collected information about demographics, pregnancy history, partner characteristics, and psychosocial factors through questionnaires administered in Kiswahili, Dholuo, or English languages using REDCap surveys. Experience of depressive symptoms was collected during pregnancy (enrollment visit) using the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10). Participants rated each of 10 items from 0-3 based on past-week frequency (absolute score range: 0-30). Moderate-to-severe depressive symptoms (MSD) was defined as a validated cut-point of 10 or greater (CESD-10 score $\geq$ 10).[170] Mild-to-severe depressive symptoms (Mild-SD), defined as a cut-point of 5 or greater (CESD-10 score $\geq$ 5) to identify differences between women with “any” versus “no” depressive symptoms. The 18-item

Medical Outcomes Study Social Support Survey (MOS-SSS; range: 18-90) was used to assess social support.[151] This variable was dichotomized with a cut-point of <72 denoting low social support (LSS). Scores <72 indicate that women reported not having access "most of the time" to all forms of social support. The 4-item Hurt, Insult, Threaten, Scream Scale with a cut-point of 10 or greater (range: 4-20) assessed intimate partner violence (IPV).[150]

We hypothesized that multiple characteristics potentially confound the relationship between psychosocial and adverse perinatal outcomes. Household crowding was used as a marker of socioeconomic status,[155] defined as the ratio of people per room greater than the median (>2 people/room). A validated risk score, developed to predict HIV acquisition among perinatal women in SSA, was used to define high HIV risk.[169] Self-perceived risk for HIV acquisition was measured by asking participants "What is your gut feeling about how likely you are to get infected with HIV?", with five Likert response options. We defined high self-perceived HIV risk as "very or extremely likely" compared to all lower likelihood levels.[262]

Data were collected at study visits monthly during pregnancy, and at 6 weeks postpartum and three-monthly thereafter.

Outcomes

Study nurses determined gestational age at enrollment by ascertainment of last menstrual period (LMP) or fundal height. Data on birth outcomes were collected at the 6-week postpartum visit and abstracted from medical records. Information was collected about pregnancy loss (<20 weeks gestation), stillbirth (fetal death ≥20 weeks gestation), gestational age at delivery (weeks), and birthweight (kilograms). Late stillbirth was defined as fetal death ≥28 weeks gestation. Infant low birthweight (LBW) was defined as weight <2.5 kilograms[263] and small-for-gestational age (SGA) was defined using the World Health Organization (WHO) Fetal Growth Standards to identify infants who were below the 10th percentile for birthweight for respective gestational age and sex at birth.[264] Verbal autopsies were performed by a study nurse with the mother or caregiver in the event of pregnancy loss or neonatal death (from birth up to 28 days post-delivery).

Statistical analysis

Participants were included in the analysis if they had information on gestational age at pregnancy outcome (implausible values >44 weeks were considered missing), did not acquire HIV during the study, had a singleton birth, and had depressive symptom information during pregnancy. Incidence of pregnancy loss and stillbirth were evaluated among those enrolled <20 weeks gestation to alleviate selection bias. Similarly, late stillbirth was assessed among those enrolled at <28 weeks gestation. PTB incidence was assessed among participants enrolled at <37 weeks gestation. Infant LBW and SGA analyses were limited to live births with infant birthweight data available. Neonatal mortality was evaluated among all live births.

Two different definitions were used for “any adverse perinatal outcome” among different sub-groups: 1) occurrence of pregnancy loss, stillbirth, PTB, or neonatal death among all eligible pregnancies, We estimated the risk of having pregnancy loss, stillbirth, preterm birth, or neonatal death among all pregnancies (n=4153) to assess occurrence of any perinatal outcome in the most inclusive number of pregnancies to optimize statistical power for associations. 2) We separately assessed occurrence of pregnancy loss, stillbirth, preterm birth, LBW, SGA, or neonatal death in a more restricted group of pregnancies enrolled <20 weeks gestation with birthweight data for livebirths (n=624) (Figure 6.1). By evaluating the most- and least-inclusive groups for any adverse outcome, we offer a reasonable range of risk for any adverse perinatal outcome.

Cox proportional hazards models were used to assess relationships between psychosocial factors of depressive symptom score, mild-SD, MSD, LSS, and IPV with time-to-adverse perinatal outcome, clustered by facility. When case counts were <5, regression analyses were not performed. Time from enrollment gestational age to gestational age at adverse perinatal outcome was used for time-at-risk for cases, except for the neonatal death analyses which used time from birth. Time-at-risk for non-cases was gestational age at the end of the at-risk period or gestational age at pregnancy end, whichever came first. Gestational age at enrollment served as the start time to account for left truncation.[265] Start time was set at 20 weeks gestation for the

stillbirth analysis and 28 weeks gestation for the late stillbirth analysis based on the at-risk period for those outcomes. In the "any adverse perinatal outcome" analyses, survival time to neonatal death was gestational age plus time from birth to death (cases) and gestational age plus 28 days postpartum (non-cases).

Variables hypothesized as confounders were included in multivariable models, as depicted in our conceptual model (Appendix).[19,80,81,266] Maternal age (years), educational attainment (years), regular employment, being married or living with a partner, household crowding (≥2 people/room), multiparity, prior adverse perinatal outcome (pregnancy loss, stillbirth, or preterm birth), high HIV risk (Pintye et al. risk score >6 vs. ≤ 6), self-perceived high HIV risk (extremely/very likely vs somewhat/very/extremely unlikely), PrEP uptake in pregnancy, and ANC attendance (Total visits attended by enrollment [pregnancy loss analysis], ≥4 ANC visits attended vs. <4 ANC visits [all other analysis]) were included. We additionally included gestational age at enrollment (weeks) in the LBW and SGA analyses (not in Cox regression models since gestational age was incorporated as start time). In each model, the two psychosocial factors that were not being evaluated as the main exposure (MSD, low social support, and/or intimate partner violence) were included. Multivariable analyses were performed for relationships between psychosocial factors and adverse perinatal outcomes significant in univariable analyses at p-value ≤0.10. Population attributable risk percentages (PAR%) were estimated for each psychosocial risk factor of an adverse perinatal outcome (p-value ≤0.05); we did not calculate PAR% for protective factors or continuous variables.

For participants missing data in <5 out of 10 depressive symptom scale items (11.8%, 492/4185, Appendix), item-level scores were imputed as the median score across the participant's existing items (person-median imputation).[267] Among those missing <8 out of 16 social support scale items (2.6%, 108/4185, Appendix), we imputed item-level scores using person-median imputation. Analyses were conducted using Stata 15.

Ethical considerations

The study protocol, informed consent forms, and data collection tools were approved by the Kenyatta National Hospital-University of Nairobi Ethics Research Committee and University of Washington Human Subjects Review Committee. Approval was obtained from Siaya and Homabay county Department of Health and facility administrators. All participants provided written informed consent.

Role of funding sources

Funding agencies had no role in writing this manuscript or submitting for publication.

Results

Overall, 93% (n=4153) of the 4447 pregnant women enrolled in the parent study met inclusion criteria for this analysis (Figure 6.1). Median maternal age was 24 years (Interquartile range [IQR]: 21-28), median gestational age at enrollment was 24 weeks (IQR: 20-30), and median educational attainment 10 years (IQR: 8-12) (Table 6.1). The majority of participants were married or living with their partner (84.8%, 3491/4118) and were multiparous (74.3%, 3083/4148). Half of the women (50.5%, 2098/4153) attended their first ANC visit during the second trimester, and most women (88%, 3655/4153) attended at least 4 ANC visits before pregnancy end.

About a quarter (23.9%, 994/4153) of women reported MSD during pregnancy (median CESD-10 score: 5, IQR: 3-9). Over 50% of women reported mild-SD (54.7%, 2273/4153). Over a third (37.3%, 1550/4153) had low social support (median MOS-SSS score: 75, IQR: 63-88), and 8% reported IPV in the two weeks prior to enrollment (7.8%, 323/4148).

Pregnancy loss was experienced by 1.5% (15/1005) of women enrolled <20 weeks gestation, over 111.3 person-years of follow-up until 20 weeks gestation (Incidence rate [IR]: 13.5 pregnancy losses per 100 person-years, 95% confidence interval [CI]:8.1-22.4) (Appendix). Median gestational age at pregnancy loss was 15.0 weeks (IQR:12.1-17.7). Women reporting MSD were over twice as likely to experience pregnancy loss compared to those without MSD (Hazard Ratio [HR]: 2.8, 95% CI:1.3-5.9, p=0.007) (Figure 6.2). This relationship strengthened with confounding adjustment (adjusted Hazard Ratio [aHR]: 5.0, 95% CI: 2.4-10.4 p<0.001)

(Table 6.3). A ten-unit increase in CESD-10 score was associated with 70% higher risk of pregnancy loss (HR: 1.7, 95% CI: 1.1-2.7, p=0.011; aHR: 2.6, 95% CI: 1.7-3.9, p<0.001). There was no difference in pregnancy loss risk between those with mild-SD versus no depressive symptoms. Pregnancy loss case counts were too low (<5) when stratified by low social support and IPV to support regression analyses.

Overall, 3.2% (32/990) of women enrolled <20 weeks gestation experienced stillbirth over 337.9 person-years of follow-up starting at 20 weeks gestation (IR: 9.5 stillbirths per 100 person-years, 95% CI: 6.7-13.4). Stillbirths occurred at a median gestational age of 35.4 weeks (IQR: 25.6-38.3). Women reporting low social support (LSS) had double the risk of stillbirth (HR: 2.1, 95% CI: 1.0-4.1, p=0.041; aHR: 2.4, 95% CI: 1.1-4.9, p=0.021). Late stillbirth occurred in 1.8% (47/2566) of women enrolled <28 weeks gestation over 542.5 person-years (IR: 8.7 per 100 person-years, 95% CI: 6.5-11.5). There was a trend toward significance for the relationship between LSS and f late stillbirth in univariable analysis (p=0.054) which was not retained after adjustment (p=0.196). There was no evidence of relationships between MSD, mild-SD, CESD-10 score, or IPV with stillbirth or late stillbirth.

PTB occurred among 19.1% (780/4084) of mother-infant pairs enrolled <37 weeks gestation over 1099.3 person-years of follow-up (IR: 70.9 preterm births per 100 person-years, 95% CI: 66.1-76.1) and at median gestational age of 36.0 weeks (IQR: 35.3-36.0). Mild-SD was associated with increased risk for preterm birth (HR: 1.5, 95% CI: 1.1-1.9, p=0.016; aHR: 1.4, 95% CI: 1.0-1.9, p=0.034). There was a trend for higher CESD-10 scores associated with higher risk of PTB (HR: 1.2, 95% CI: 0.9-1.5, p=0.063), which was not significant after adjustment (p=0.104). IPV in pregnancy was inversely related to risk of PTB (HR: 0.8, 95% CI: 0.6-0.9, p=0.044), with a trend in adjusted analysis (p=0.055). MSD and LSS were not associated with risk of PTB.

Overall, 64.7% (2627/4055) of livebirths had birthweight data, among which 2.3% (60/2625, 95% CI: 1.8-2.9) of infants had LBW. Women with mild-SD had nearly twice the risk of

LBW (Relative Risk [RR]: 1.8, 95% CI: 1.2-2.8, p=0.008; adjusted RR [aRR]: 1.9, 95% CI: 1.2-3.0, p=0.006). A ten-unit higher CESD-10 score was associated with double the risk of LBW (RR: 1.5, 95% CI: 1.1-2.0, p=0.004, aRR: 2.0, 95% CI: 1.2-3.4, p=0.008). There was no evidence of relationships between MSD or LSS with LBW. About 10.0% (263/2627, 95% CI: 8.9-11.2) of infants with birthweight information were SGA. No psychosocial factors were associated with SGA.

Among 4,055 live births, 66 deaths occurred in the first 28 days postpartum, amounting to a cumulative mortality of 16 deaths per 1000 live births. Neonatal deaths took place over 306.6 person-years (IR: 20.5 cases per 100 person-years, 95% CI: 16.0-26.3). Median age at neonatal death was 1 day (IQR: 0-7.5). There was no evidence of relationships between psychosocial factors and neonatal mortality.

Over a quarter (27.3%, 1132/4153) of pregnancies resulted in at least one adverse perinatal outcome, for an incidence rate of 63.8 per 100 person years (95% CI: 59.6-68.2). Any adverse perinatal outcome was more likely with maternal mild-SD (HR: 1.4, 95% CI: 1.1-1.9, p=0.017, aHR: 1.3, 95% CI: 1.0-1.9, p=0.034), and a 10-unit higher CESD-10 score (aHR: 1.3, 95% CI: 1.0-1.6, p=0.032). In the subset of mother-infant pairs enrolled <20 weeks gestation with birthweight data, 32.2% (201/625) had any adverse perinatal outcome for an incidence rate of 64.7 per 100 person-years. Risk of any adverse outcomes was higher among women reporting low social support than those with higher social support (HR: 1.6, 95% CI: 1.3-1.9, p<0.001, aHR: 1.6, 95% CI: 1.2-1.9, p<0.001).

Based on population attributable risk proportions, over a third of pregnancy losses (37.4%, 95% CI: 30.3-43.8) were attributable to MSD (Table 6.3), and a third of stillbirth cases (33.9%, 95% CI: 9.9-51.5) were attributable to low social support. About 30% of LBW cases (95% CI: 11.9-44.1), 18% of PTB (95% CI: 2.6-30.3), and 17% of any adverse perinatal outcome cases (95% CI: 2.6-30.3) were attributable to having mild-SD. Among those enrolled <20 weeks

gestation and with birthweight data, 14% of any adverse perinatal outcome cases (95% CI: 8.0-19.6) were attributable to low social support.

Prior to imputing CESD-10 and MOS-SSS items for partial scores (missing <50% of items), 24.6% (900/3659) of women had MSD (median CESD-10 score: 5, IQR: 3-9) and 36.9% (1504/4075) of women had low social support (median social support score: 75, IQR: 63-88). Those with complete vs. partial CESD-10 data were not meaningfully different in most factors evaluated (Appendix).

Discussion

In this large prospective analysis among mother-infant pairs followed from pregnancy through 28 days postpartum, mild- or moderate-to-severe depressive symptoms during pregnancy were common and associated with increased pregnancy loss and LBW. Risk of stillbirth was elevated among women with low social support. Our results extend the global evidence-base for the impact of maternal mental distress on adverse perinatal outcomes, adding novel results on psychosocial factors and birth outcomes to the dearth of data from the African region on this topic. To our knowledge, this is the largest study to evaluate relationships between maternal mental health and >3 birth outcomes among African mother-infant pairs.[261] Our findings that maternal depressive symptoms increase risk of pregnancy loss, PTB, and LBW, and that lack of social support increased risk of stillbirth, highlight the need for integrated mental health services within maternal child health (MCH) settings to improve mother-infant outcomes.

We found about a quarter (24%) of women were depressed during pregnancy, which closely aligned with the pooled prevalence from a recent meta-analysis of antenatal depression in Africa (26%). [162] Low social support (37%) and IPV (8%) during pregnancy were also similar to estimates from other studies among pregnant women in SSA (23%,[268] 13.5%,[269] respectively). Half of women enrolled in this study initiated ANC during the second trimester, similar to national findings for Kenya (median gestational month of initial ANC: 5.4).[140]

Pregnancy loss incidence rates are not routinely evaluated in SSA. Our finding of 15 pregnancy losses per 1000 pregnancies was about double the estimate from a Kenyan study using the Nairobi Urban Health and Demographic Surveillance System,[270] likely due to underreporting and ascertainment challenges within the health system. Our estimate of pregnancy loss aligns with estimates from settings with more advanced monitoring systems for this outcome.[271] We estimated 32.4 stillbirths per 1000 pregnancies which was also higher than regional estimates (20.5 per 1000 pregnancies).[257] In our study, PTB occurred in 19% of births, slightly higher than the 12% estimated for SSA overall.[272,273] We found 2.3% of infants had LBW, lower than UNICEF's 2015 estimate of 13.4% for East Africa,[274] potentially due to a high amount of missing birthweight data in our study (~35%). About 10% of infants in our study were small-for-gestational age – also lower than global estimates for SSA.[275] Our finding that 16 neonatal deaths occur per 1000 live births was slightly lower than a 2015 estimate of 22 deaths per 1000 live births.[276]

In this large cohort of mother-infant pairs, maternal depressive symptoms in pregnancy were associated with multiple adverse birth outcomes – some confirming results from other contexts, others offering new insights. To date, few studies have evaluated associations between depression during pregnancy and pregnancy loss[277,278], likely due to challenges with statistical power and timing of measurement. The PrIMA study enrolled >1000 pregnant women before 20 weeks gestation who were evaluated for pregnancy loss, among whom pregnancy loss risk was substantially increased (5-times) with MSD. This was the largest effect size for a relationship between a psychosocial factor and adverse birth outcome in our study; we found nearly 40% of pregnancy losses could be potentially prevented if MSD in pregnancy was eliminated in this population. Pregnancy loss risk increased with higher depressive symptom score, strengthening inference regarding this relationship. Maternal depressive symptoms may impact pregnancy loss through physiologic mechanisms such as a heightened stress hormones , and/or through

behavioral responses to depressive symptoms such as inadequate nutrition, and lower health-seeking behavior.[279]

As in similar studies, depressive symptoms were not associated with stillbirth risk in our study. However, stillbirth incidence was double among women reporting low social support. We estimated about 30% of stillbirths in the population were attributable to low social support. We are not aware of other studies identifying this relationship, though a similar study in Ethiopia found an association between low social support and low birthweight.[258] Social support is modifiable with low-intensity, evidence-based psychological interventions integrated in routine MCH care.[280] We noted that the effect of low social support on stillbirth was slightly attenuated in a model adjusted for ANC attendance (≥4 ANC visits vs fewer). Integrating peer support and psychosocial services into MCH care, particularly ANC services, could prevent pregnancy loss.

There is a strong global evidence-base for the influence of depression during pregnancy on risk of preterm birth.[32,33,248], including one study from Kenya.[260] We found an association between mild-to-severe depressive symptoms and PTB. A study in Ghana also found a potential relationship that was not statistically significant.[259] There is need for further study of associations between depression and PTB in SSA where >25% of the world's preterm births occur.[272] We found a counterintuitive trend of lower PTB among women with IPV in pregnancy in contrast to findings from other East African settings.[281,282] This finding was not retained in multivariate analyses and potentially explained by collider stratification bias.

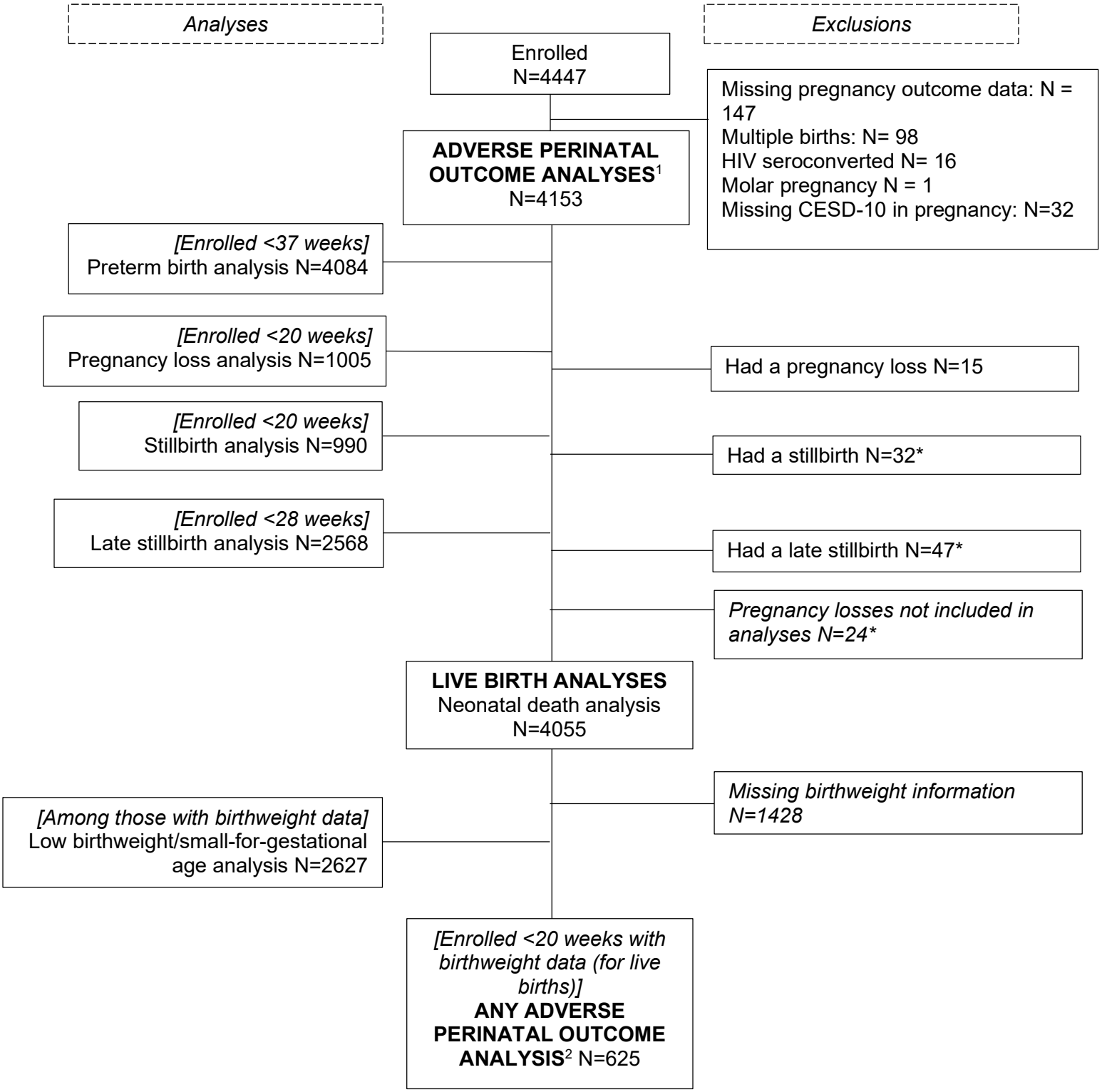
Risk of LBW is substantially higher among depressed pregnant women in multiple global contexts,[33,248] including one study from Ethiopia.[258] Women with mild-to-severe depressive symptoms had twice the risk of having a LBW infant than those with no depressive symptoms in our study. We estimated 34% of LBW cases would be averted if depressive symptoms in pregnancy were alleviated. Higher depressive symptom score was also associated with risk of LBW infants, further bolstering our finding. LBW infants have substantially higher mortality risk.[274]

Alleviating maternal depressive symptoms in pregnancy could improve neonatal survival, particularly in regions with persisting high neonatal death.

The present study had important strengths and limitations. Prospective data from >4000 pregnant women enabled rigorous evaluation of relationships between multiple psychosocial factors and adverse birth outcomes. However, for particularly rare perinatal outcomes and infrequent exposures, our study may have had modest power to detect associations. Our study did not include measurement of anxiety symptoms, which are frequently comorbid with depression and influence adverse perinatal outcomes. We estimated gestational age – which served as survival time for most birth outcomes -- as the time between last menstrual period and pregnancy end. LMP tends to overestimate gestational age which may have biased our risk estimates.[283] However, a recent study in South Africa found LMP provided a reliable and valid estimate of gestational age compared to ultrasound (within 0.2 days).[284] We used person-median imputation for CESD-10 and MOS-SSS items among participants missing fewer than half of scale items (12% and 2% of participants, respectively). In simulation studies, this method performs indistinguishably from multiple imputation of item-level psychosocial scale missingness and is recommended to optimize analytic power. We evaluated each relationship between a psychosocial factor and birth outcome independently, without accounting for multiple testing as this is an exploratory analysis aimed at identifying associations for evaluation in future studies.

In conclusion, our study contributes new evidence for the impact of maternal mental distress on birth outcomes contributing to high pregnancy loss and neonatal mortality in LMIC. Closing the “last mile” in neonatal health should include integrating mental health services into MCH care settings to reduce maternal depression and depression-related neonatal outcomes. Psychosocial interventions that increase social support and alleviate depressive symptoms may substantially reduce pregnancy loss, stillbirth, PTB, and LBW, ultimately improving linked mother-infant health.

Figure 6.1. Flow diagram for study population



*The stillbirth cases included in the "stillbirth" analysis and "late stillbirth" analysis overlap by N=20. There were N=24 stillbirths not included in either stillbirth analysis based on ineligible enrollment age.

[1]Any adverse perinatal outcome: pregnancy loss, stillbirth, preterm birth, low birthweight, small for gestational age, or neonatal death; among those enrolled <20 weeks and with birthweight data (for live births)

[2]Any adverse perinatal outcome: pregnancy loss, stillbirth, preterm birth, or neonatal death; among all eligible pregnancies

Table 6.1. Baseline characteristics of PrIMA study participants included in MSD-birth outcomes analysis

	Overall (n=4153)		MSD (n=994)		No MSD (n=3159)	
Demographic characteristics	**N**	n (%) or Median (IQR)	**n**	n (%) or Median (IQR)	**n**	n (%) or Median (IQR)
Age (years)	4151	24 (21, 28)	994	24 (21, 29)	3158	24 (21, 29)
Adolescents and young women (<24 years)	4151	2370 (57.1%)	994	566 (57.0%)	3158	1804 (57.1%)
Gestational age (enrollment, weeks)	4153	24 (20, 30)	994	24 (20, 30)	3159	24 (20, 30)
Married or living with a partner	4119	3491 (84.8%)	987	812 (82.4%)	3132	2679 (85.5%)
Completed education (years)	4074	10 (8, 12)	971	10 (8, 12)	3101	10 (8, 12)
Regularly employed	4101	612 (14.9%)	982	121 (12.3%)	3119	491 (15.7%)
Household crowding (≥2 people/room)	4126	1995 (48.4%)	989	532 (53.8%)	3137	1463 (46.6%)
Pregnancy history & factors						
Multiparous	4148	3083 (74.3%)	994	758 (76.4%)	3159	2325 (73.7%)
Prior pregnancy loss	4139	539 (13.0%)	987	150 (15.2%)	3158	389 (12.3%)
Prior preterm birth	4153	42 (1.0%)	985	8 (0.8%)	3125	34 (1.1%)
Trimester of initial antenatal care (ANC) visit	4153		994		3159	
First		615 (14.8%)		128 (12.9%)		487 (15.4%)
Second		2098 (50.5%)		500 (50.3%)		1598 (50.6%)
Third		1440 (34.7%)		366 (36.8%)		1074 (34.0%)
Attended at least 4 ANC visits (before pregnancy end)	4153	3655 (88.0%)		876 (88.1%)		2779 (88.0%)
Infant sex (female)	3617	1840 (50.9%)	866	443 (51.2%)	2752	1398 (50.8%)
HIV risk factors						
High HIV risk[a]	4153	1542 (37.1%)	994	454 (45.7%)	3159	1088 (34.4%)
Self-perceived HIV risk	4146	369 (8.9%)	993	124 (12.5%)	3153	245 (7.8%)
Lifetime sexual partners	4148	2 (2, 3)	994	3 (2, 4)	3154	2 (2, 3)
Lifetime sexual partners (>2)	4148	3448 (83.1%)	994	871 (87.6%)	3154	2577 (81.7%)
Partner age difference >10 years*	3184	497 (15.6%)	736	118 (16.0%)	2446	379 (15.5%)
Partner HIV-positive	4001	176 (4.3%)	979	67 (6.8%)	3122	109 (3.5%)
Partner HIV status unknown	4001	1296 (31.6%)	979	370 (37.8%)	3122	926 (29.7%)
Sexually transmitted infection (enrollment)	4146	104 (2.5%)	992	45 (4.5%)	3154	59 (1.9%)
PrEP Use in pregnancy	4153	551 (13.3%)	994	192 (19.3%)	3159	359 (11.4%)
Psychosocial characteristics						
Ever drink alcohol	4135	168 (4.1%)	985	50 (5.1%)	3151	118 (3.7%)
Social support score[b]	4153	75 (63, 88)	994	70 (56, 81)	3159	78 (66, 89)
Low social support (MOS-SSS score <72)	4153	1550 (37.3%)	994	521 (52.4%)	3159	1029 (32.6%)
Intimate partner violence[c] (HITS score ≥10)	4148	323 (7.8%)	993	170 (17.1%)	3155	153 (4.8%)
CESD-10 score	4153	5 (3, 9)	994	13 (11, 16)	3159	4 (2, 6)
Mild-to-severe depressive symptoms (CESD-10≥5)	4153	2273 (54.7%)	994	994 (100%)	3159	1279 (40.5%)
Moderate-to-severe depressive symptoms (CESD-10≥10)	4153	994 (23.9%)		--		--

*Among those with current partners

[a]We evaluated HIV risk using the Pintye et al.[169] risk score (high HIV risk: score >6 = "Yes", score ≤6 = "No").

[b]We evaluated social support using the 18-item Medical Outcomes Study social support score (MOS-SSS), defining low social support as scores below 72 (Low social support: MOS-SSS score score <72 = "Yes", MOS-SSS score ≥ 72 = "No").

[c]We evaluated intimate partner violence using the 4-item Hurt, Insult, Threaten, and Scream scale (HITS), defining intimate partner violence as scores of 10 and above (IPV: HITS score ≥10 = "Yes", HITS score <10 = "No").

CESD-10: Center for epidemiologic studies depression scale-10

MSD: Moderate-to-severe depressive symptoms

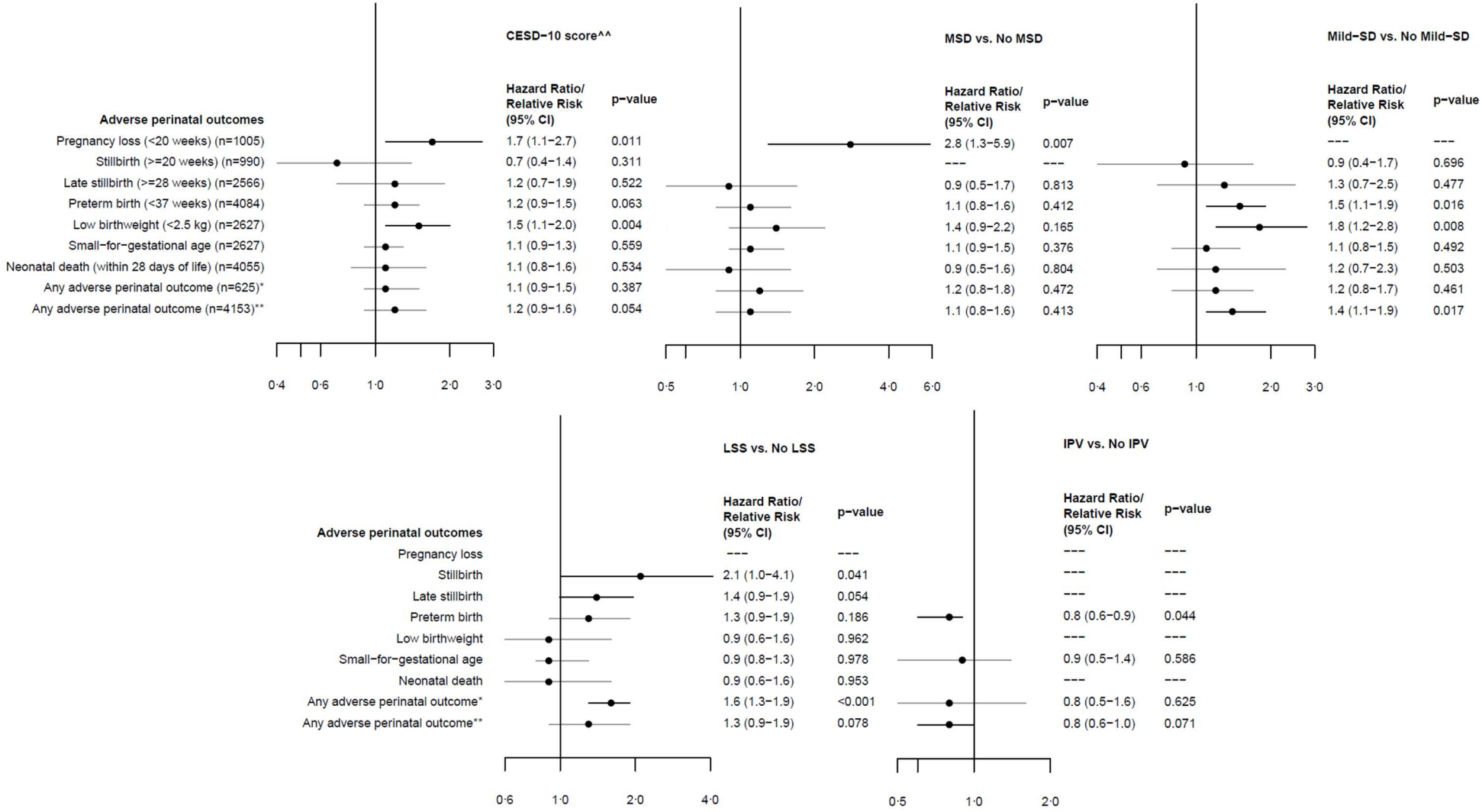
Table 6.2. Cumulative incidence of adverse perinatal outcomes among pregnant and postpartum women in Western Kenya

Adverse perinatal outcomes	Exposed	Cases	N	Cumulative incidence (CI) per 1000 pregnancies	95% Confidence interval (CI)	Unexposed	Cases	N	CI per 1000 pregnancies	95% CI
Pregnancy loss	Overall	15	990	15	8.1-22.4					
(<20 weeks)	MSD	7	223	31.4	14.9-64.6	No MSD	8	782	10.2	5.1-20.3
(n=1005)	Mild-SD	10	525	19.0	10.3-35.1	No Mild-SD	5^	480	10.4	4.3-24.8
	LSS	2^	333	6.0	1.5-23.8	No LSS	13	672	19.3	11.3-33.1
	IPV	1^	80	12.5	1.7-85.8	No IPV	14	925	15.1	8.9-25.4
Stillbirth	Overall	32	990	32.3	22.9-45.4					
(≥ 20 weeks)	MSD	4^	216	18.5	6.9-48.5	No MSD	28	774	36.2	25.1-51.9
(n=990)	Mild-SD	15	515	29.1	17.6-47.8	No Mild-SD	17	475	35.8	22.3-56.9
	LSS	16	331	48.3	29.8-77.6	No LSS	16	659	24.3	14.9-39.2
	IPV	3^	79	37.9	12.1-113.0	No IPV	29	911	31.8	22.2-45.5
Late stillbirth	Overall	47	2568	18.3	13.8-24.2					
(≥28 weeks)	MSD	11	600	18.3	10.2-32.8	No MSD	36	1968	18.3	13.2-25.2
(n=2566)	Mild-SD	28	1422	19.7	13.6-28.4	No Mild-SD	19	1146	16.6	10.6-25.9
	LSS	21	903	23.3	15.2-35.4	No LSS	26	1665	15.6	10.7-22.8
	IPV	4^	200	20.0	7.5-52.4	No IPV	43	2364	18.2	13.5-24.4
Preterm birth	Overall	780	4084	190.9	179.2-203.3					
(<37 weeks)	MSD	202	975	207.2	182.9-233.8	No MSD	578	3109	185.9	172.6-199.9
(n=4084)	Mild-SD	492	2239	219.7	203.1-237.4	No Mild-SD	288	1845	156.1	140.2-173.4
	LSS	332	1522	218.1	198.1-239.6	No LSS	448	2562	174.9	160.6-190.1
	IPV	48	318	150.9	115.5-194.8	No IPV	730	3761	194.1	181.8-207.1
Low birthweight	Overall	60	2627	228	177.7-293.1					
(<2.5 kg)	MSD	20	697	28.7	18.6-44.1	No MSD	40	1930	20.7	15.2-28.1
(n=2627)	Mild-SD	42	1484	28.3	20.9-38.1	No Mild-SD	18	1143	15.7	9.9-24.9
	LSS	20	883	22.7	14.6-34.9	No LSS	40	1744	22.9	16.9-31.1
	IPV	4^	224	17.9	6.7-46.8	No IPV	56	2401	23.3	17.9-30.2
Small-for-gestational	Overall	263	2627	100.1	89.2-112.2					
age **(n=2627)**	MSD	77	699	110.2	88.9-135.6	No MSD	186	1928	996.5	84.1-110.5
	Mild-SD	155	1486	104.3	89.7-120.9	No Mild-SD	108	1141	94.7	78.9-113.1
	LSS	88	881	99.9	81.7-121.5	No LSS	175	1746	100.2	86.9-115.2
	IPV	20	225	88.9	57.9-134.0	No IPV	243	2400	101.3	89.8-113.9
Neonatal death (within	Overall	66	4055	16.3	12.8-20.7					
28 days of life)	MSD	14	967	14.5	8.6-24.3	No MSD	52	3088	16.8	12.9-22.0
(n=4055)	Mild-SD	40	2215	18.1	13.3-24.5	No Mild-SD	26	1840	14.1	9.6-20.7
	LSS	25	1516	16.5	11.2-24.3	No LSS	41	2539	16.1	11.9-21.9
	IPV	3^	315	9.5	3.1-29.2	No IPV	63	3735	16.9	13.2-21.5
Any adverse perinatal	Overall	201	625	321.6	286.1-359.3					
outcome **(n=625)**[1]	MSD	58	163	335.8	285.7-432.8	No MSD	143	462	309.5	268.9-353.3
	Mild-SD	117	346	338.2	290.0-389.8	No Mild-SD	84	279	301.1	249.9-357.7
	LSS	79	201	393.0	327.5-462.6	No LSS	122	424	287.7	246.5-332.8
	IPV	13	49	265.3	158.5-409.0	No IPV	188	576	326.4	289.2-365.9
Any adverse perinatal	Overall	1132	4153	272.6	259.2-286.3					
outcome **(n=4153)**[2]	MSD	297	994	298.8	271.1-328.0	No MSD	835	3159	264.3	249.2-279.9
	Mild-SD	694	2273	305.3	286.7-324.6	No Mild-SD	438	1880	232.9	214.4-252.6
	LSS	447	1550	288.4	166.4-311.5	No LSS	685	2603	263.2	246.6-280.4

	IPV	75	323	232.2	189.2-281.6	No IPV	1055	3825	275.8	261.9-290.2

^For instances with case counts ≤5 in an exposure group, we did not perform regression analyses
[1]Any adverse perinatal outcome: pregnancy loss, stillbirth, preterm birth, low birthweight, small for gestational age, or neonatal death; among those enrolled <20 weeks and with birthweight data (for live births)
[2]Any adverse perinatal outcome: pregnancy loss, stillbirth, preterm birth, or neonatal death; among all eligible pregnancies
CESD-10: Center for epidemiologic studies depression scale-10
CI: Cumulative Incidence per 1000 pregnancices
Mild-SD: Mild-to-severe depressive symptoms
MSD: Moderate-to-severe depressive symptoms
LSS: Low social support
IPV: Intimate partner violence

Figure 6.2. Associations between psychosocial factors and adverse perinatal outcomes



HR: Hazard ratios are from Cox Regression Models, clustered by facility used for outcomes of: pregnancy loss, stillbirth, late stillbirth, preterm birth, neonatal death, any adverse perinatal outcome
RR: Relative risks are from Poisson Regression Models with robust standard errors, clustered by facility used for outcomes of low birthweight and small-for-gestational age
For instances with case counts ≤5 in an exposure group, we did not perform regression analyses
^^CESD-10 score was re-scaled to reflect a 10-unit change in score
*Any adverse perinatal outcome: pregnancy loss, stillbirth, preterm birth, low birthweight, small for gestational age, or neonatal death; among those enrolled <20 weeks and with birthweight data (for live births)
**Any adverse perinatal outcome: pregnancy loss, stillbirth, preterm birth, or neonatal death; among all eligible pregnancies
CESD-10: Center for epidemiologic studies depression scale-10
Mild-SD: Mild-to-severe depressive symptoms
MSD: Moderate-to-severe depressive symptoms
LSS: Low social support
IPV: Intimate partner violence

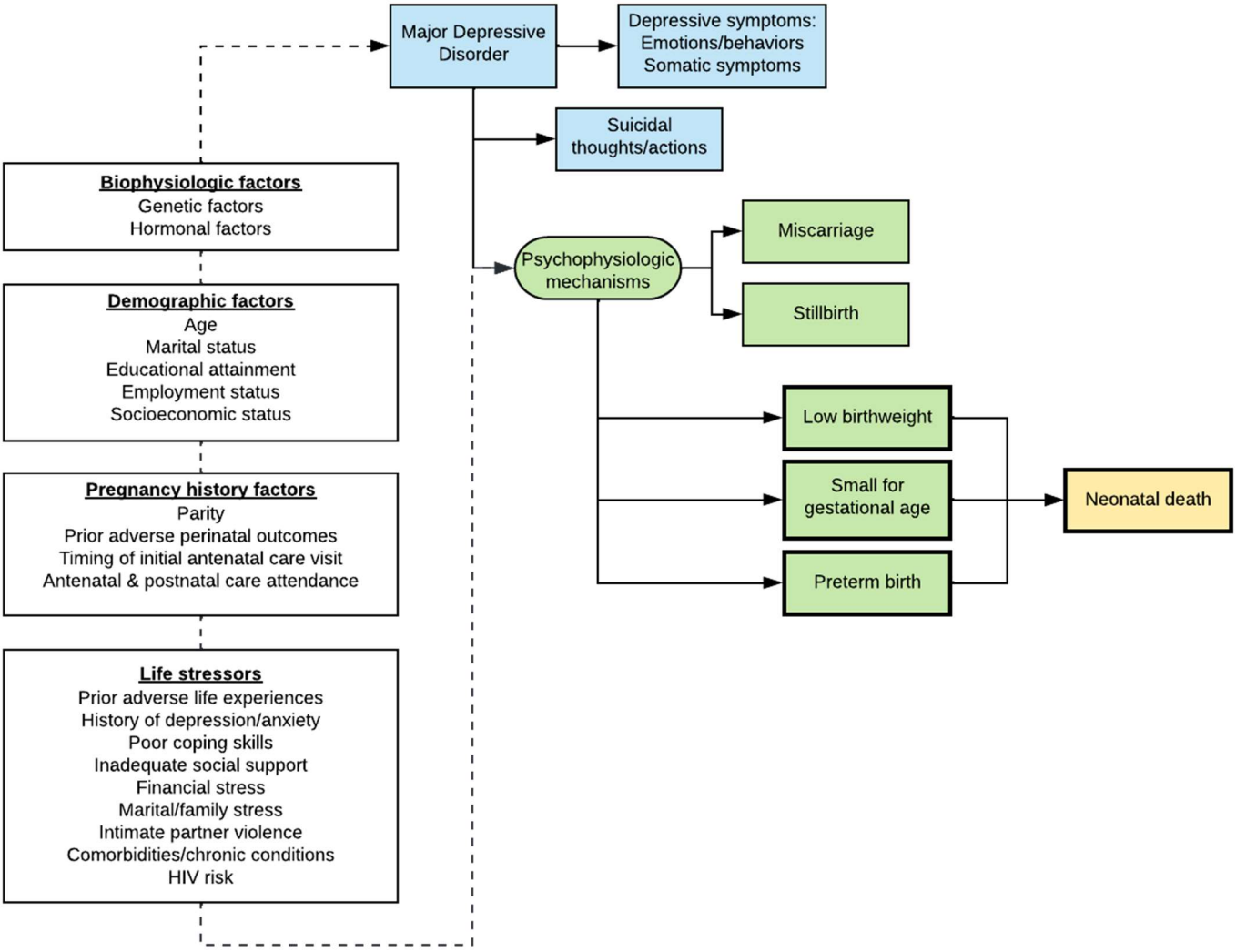
Table 6.3. Psychosocial correlates of adverse perinatal outcomes and population attributable risk percentages

	Univariable Analysis[1]			Multivariable Analysis			Population attributable risk percent (PAR%)	
	HR/RR*	**95% CI**	**p-value**	**aHR/RR****	**95% CI**	**p-value**	**PAR%**	**95% CI**
Exposure: CESD-10 score^								
Pregnancy loss (n=1005)	1.7	1.1-2.7	0.011	**2.6**	**1.7-3.9**	**<0.001**		
Preterm birth (n=4084)	1.2	0.9-1.5	0.063	1.2	0.9-1.6	0.104		
Low birthweight (n=2627)	1.5	1.1-2.0	0.004	**2.0**	**1.2-3.4**	**0.008**		
Any adverse perinatal outcome (n=4153)[2]	1.2	0.9-1.6	0.054	**1.3**	**1.0-1.6**	**0.032**		
Exposure: Mild-SD vs No Mild-SD								
Preterm birth (n=4084)	1.5	1.1-1.9	0.016	**1.4**	**1.0-1.9**	**0.034**	17.3%	2.6-29.8
Low birthweight (n=2627)	1.8	1.2-2.8	0.008	**1.9**	**1.2-3.0**	**0.006**	33.9%	9.9-51.5
Any adverse perinatal outcome (n=4153)	1.4	1.1-1.9	0.017	**1.4**	**1.0-1.9**	**0.034**	17.6%	2.6-30.3
Exposure: MSD vs. No MSD								
Pregnancy loss (n=1005)	2.8	1.3-5.9	0.007	**5.0**	**2.4-10.4**	**<0.001**	37.4%	30.3-43.8
Exposure: LSS vs. higher social support								
Stillbirth (n=990)	2.1	1.0-4.1	0.041	**2.4**	**1.1-4.9**	**0.021**	29.9%	11.9-44.1
Late stillbirth (n=2566)	1.4	0.99-1.97	0.054	1.3	0.9-1.9	0.196		
Any adverse perinatal outcome (n=625)[3]	1.6	1.3-1.9	<0.001	**1.6**	**1.2-1.9**	**<0.001**	14.0%	8.0-19.6
Any adverse perinatal outcome (n=4153)	1.3	0.9-1.9	0.078	1.3	0.9-1.8	0.069		
Exposure: IPV vs. No IPV								
Preterm birth (n=4084)	0.8	0.6-0.9	0.044	0.7	0.5-1.0	0.055		
Any adverse perinatal outcome (n=4153)[2]	0.8	0.6-1.0	0.071	0.8	0.6-1.0	0.096		

[1]This table contains results from univariable analysis significant at alpha<0.10
[2]Any adverse perinatal outcome: pregnancy loss, stillbirth, preterm birth, low birthweight, small for gestational age, or neonatal death; among those enrolled <20 weeks and with birthweight data (for live births)
[3]Any adverse perinatal outcome: pregnancy loss, stillbirth, preterm birth, or neonatal death; among all eligible pregnancies
^ CESD-10 score was re-scaled to reflect a 10-unit change in score
*Hazards Ratios (HR) estimated from Cox Regression, clustered by site; Relative Risks (RR) estimated from Poisson Regression with robust standard errors, clustered by site
**Adjusted HRs/RRs were estimated from models including: the exposure of interest (CESD-10 score, Mild-SD, MSD, LSS, IPV) and maternal age (years, continuous), educational attainment (years, continuous), regular employment (yes/no), married/living with a partner (yes/no), household crowding (yes/no), multiparous (yes/no), prior adverse perinatal outcome (pregnancy loss, stillbirth, or preterm birth, yes/no), high HIV risk (yes/no), self-perceived high HIV risk (Extremely/very likely vs Somewhat/very/extremely unlikely), PrEP uptake in pregnancy (yes/no), ANC attendance (Total visits attended by enrollment [pregnancy loss analysis], ≥4 ANC visits attended vs. <4 ANC visits [all other analysis]), and (the other psychosocial factors (MSD, low social support, or intimate partner violence). Poisson models also included gestational age at enrollment (weeks, continuous)
CESD-10: Center for epidemiologic studies depression scale-10
Mild-SD: Mild-to-severe depressive symptoms
MSD: Moderate-to-severe depressive symptoms
LSS: Low social support
IPV: Intimate partner violence

APPENDIX.

Conceptual model for the relationship between depression and adverse perinatal outcomes



References for figure components: Major depressive disorder, depressive symptoms (Fisher); Predictors of peripartum depression (Fisher, Stein, Lancaster); psychophysiologic mechanisms (Payne); Low birthweight (Jarde, Grigoriadis); Small for gestational age (Jarde), Preterm birth (Jarde, Grote, Grigoriadis); Infant death (Jacques)

Number of CESD-10 items missing among singleton births with pregnancy outcome data among women who did not acquire HIV by 9 months postpartum (n=4185)

Number of CESD-10 items missing	N (%)
0	3661 (87.48%)
1	259 (6.19%)
2	152 (3.63%)
3	67 (1.60%)
4	14 (0.33%)
5	7 (0.17%)
6	2 (0.05%)
7	1 (0.02%)
8	1 (0.02%)
9	0 (0.00%)
10	21 (0.50%)

Number of CESD-10 items missing among singleton births with pregnancy outcome data among women who did not acquire HIV by 9 months postpartum (n=4185)

Number of MOS-SSS items missing	N (%)
0	4077 (97.42%)
1	80 (1.91%)
2	7 (0.17%)
3	3 (0.07%)
4	18 (0.43%)

Baseline characteristics of PrIMA study participants among those with complete CESD-10 information versus partial (n=4153)

	Overall (N=4153)	**Complete CESD-10** (N=3659)	**Incomplete CESD-10** (N=492)	
Demographic characteristics	n (%) or Median (IQR)	n (%) or Median (IQR)	n (%) or Median (IQR)	
Age (years)	24 (21, 28) (n=4151)	24 (21, 29) (n=3659)	24 (21, 28) (n=492)	0.23
Adolescents and young women (<24 years)	2370 (57.1%)	2081 (56.8%)	289 (58.7%)	0.43
Missing	2 (<1%)	2 (0.1%)	0 (0.0%)	
Gestational age (enrollment, weeks)	24 (20, 30) (n=4153)	24 (20, 30) (n=3661)	26 (18.285714, 30) (n=492)	0.28
Married or living with a partner	3491 (84.1%)	3083 (84.2%)	408 (82.9%)	0.27
Missing	34 (0.8%)	33 (0.9%)	1 (0.2%)	
Completed education (years)	10 (8, 12) (n=4072)	10 (8, 12) (n=3589)	10 (8, 12) (n=483)	0.34
Regularly employed	612 (14.7%)	517 (14.1%)	95 (19.3%)	0.002
Missing	52 (1.3%)	44 (1.2%)	8 (1.6%)	
Household crowding (≥2 people/room)	1995 (48.0%)	1771 (48.4%)	224 (45.5%)	0.20
Missing	27 (0.7%)	26 (0.7%)	1 (0.2%)	
Pregnancy history & factors				
Multiparous	3082 (74.2%)	2735 (74.7%)	348 (70.7%)	0.062
Missing	5 (0.1%)	4 (0.1%)	1 (0.2%)	
Prior pregnancy loss	539 (13.0%)	468 (12.8%)	71 (14.4%)	0.30
Missing	14 (0.3%)	12 (0.3%)	2 (0.4%)	
Prior preterm birth	42 (1.0%)	35 (1.0%)	7 (1.4%)	0.33
Trimester of initial antenatal care (ANC) visit				
First	615 (14.8%)	523 (14.3%)	92 (18.7%)	<0.001
Second	2098 (50.5%)	1894 (51.7%)	204 (41.5%)	
Third	1440 (34.7%)	1244 (34.0%)	196 (39.8%)	
Infant sex (female)	1841 (44.3%)	1632 (44.6%)	209 (42.5%)	0.62
Missing	535 (12.9%)	463 (12.6%)	72 (14.6%)	
HIV risk factors				
Self-perceived high HIV risk	369 (8.9%)	320 (8.7%)	49 (10.0%)	0.35
Missing	7 (0.2%)	4 (0.1%)	3 (0.6%)	
Lifetime sexual partners	2 (2, 3) (n=4148)	2 (2, 3) (n=3656)	2 (2, 3) (n=492)	0.59
Partner HIV-positive*	176 (4.2%)	149 (4.1%)	27 (5.5%)	0.15
Missing	52 (1.3%)	49 (1.3%)	3 (0.6%)	
Sexually transmitted infection (enrollment)	104 (2.5%)	96 (2.6%)	8 (1.6%)	0.19
Missing	7 (0.2%)	5 (0.1%)	2 (0.4%)	
Psychosocial characteristics				
Low social support (MOS-SSS score <72)	1504 (36.2%)	1372 (37.5%)	132 (26.8%)	<0.001
Missing	90 (2.2%)	69 (1.9%)	21 (4.3%)	
Intimate partner violence [c] (HITS score ≥10)	323 (7.8%)	289 (7.9%)	34 (6.9%)	0.44
Missing	5 (0.1%)	5 (0.1%)	0 (0.0%)	

Incidence of adverse perinatal outcomes by psychosocial factors

					CESD-10 score*			
	Overall				Adverse perinatal outcome		Without adverse perinatal outcome	
Adverse perinatal outcomes	**Cases**	**Fetus-years or N**	**CI or IR**	**95% Confidence interval (CI)**	**Mean**	**St. Dev. (SD)**	**Mean**	**SD**
Pregnancy loss (<20 weeks) **(n=1005)**	15	111.3	13.5	8.1-22.4	8.6	6.5	6.2	5.4
Stillbirth (≥ 20 weeks) **(n=990)**	32	337.9	9,5	6.7-13.4	5.2	4.1	6.2	5.5
Late stillbirth (≥28 weeks) **(n=2566)**	47	542.5	8.7	6.5-11.5	6.8	5.4	6.3	5.4
Preterm birth (<37 weeks) **(n=4084)**	780	1099.3	70.9	66.1-76.1	6.9	5.3	6.2	5.4
Low birthweight (<2.5 kg) **(n=2627)**	60	2627	2.3	1.8-2.9	8.1	5.9	6.6	5.6
Small-for-gestational age **(n=2627)**	263	2627	10.0	8.9-11.2	6.8	5.5	6.6	5.6
Neonatal death (within 28 days of life) **(n=4055)**	63	306.8	20.5	16.0-26.3	6.6	5.4	6.3	5.4
Any adverse perinatal outcome **(n=625)**[1]	201	310.7	64.7	56.3-74.3	7.0	5.6	6.4	5.7
Any adverse perinatal outcome **(n=4153)**[2]	864	1355.1	63.8	59.6-68.2	6.9	5.3	6.2	5.4
	Mild-SD in pregnancy				**No Mild-SD in pregnancy**			
	Cases	**Fetus-years**	**CI or IR**	**95% CI**	**Cases**	**Fetus-years**	**CI or IR**	**95% CI**
Pregnancy loss	10	57.1	17.5	9.4-32.5	5*	54.1	9.2	3.8-22.2
Stillbirth	15	175.1	8.6	5.2-14.2	17	162.8	10.4	6.5-16.8
Late stillbirth	28	298.0	9.4	6.5-13.6	19	244.5	7.8	4.9-12.2
Preterm birth	492	596.1	82.5	75.6-90.2	288	503.2	57.2	50.9-64.2
Low birthweight	42	1442	2.8	2.1-3.8	18	1125	1.6	0.9-2.5
Small-for-gestational age	155	1486	10.4	8.9-12.1	108	1141	9.5	7.9-11.3
Neonatal death	38	167.4	22.7	16.5-31.2	25	139.4	17.9	12.1-26.5
Any adverse perinatal outcome (n=625)[1]	117	170.9	68.4	57.1-82.0	84	139.7	60.1	48.5-74.4
Any adverse perinatal outcome (n=4153)[2]	540	731.4	73.8	67.9-80.3	324	623.7	51.9	46.6-57.9
	MSD in pregnancy				**No MSD in pregnancy**			
	Cases	**Fetus-years**	**CI or IR**	**95% CI**	**Cases**	**Fetus-years**	**CI or IR**	**95% CI**
Pregnancy loss	7	25.9	27.1	12.9-56.8	8	85.4	9.4	4.7-18.7
Stillbirth	4	73.6	5.4	2.0-14.5	28	264.3	10.6	7.3-15.3
Late stillbirth	11	126.9	8.7	4.8-15.7	36	415.7	8.7	6.2-12.0
Preterm birth	202	256.8	78.7	68.5-90.3	578	842.5	68.6	63.2-74.4
Low birthweight	20	697	2.9	1.9-4.4	40	1890	2.1	1.5-2.8
Small-for-gestational age	77	699	11.0	8.9-13.6	186	1928	9.7	8.4-11.0
Neonatal death	14	73.2	19.1	11.3-32.2	49	233.5	20.9	15.9-27.8
Any adverse perinatal outcome (n=625)[1]	58	79.9	72.6	56.1-93.9	143	230.8	61.9	52.6-72.9
Any adverse perinatal outcome (n=4153)[2]	224	317.1	70.6	61.9-80.5	640	1038.1	61.7	57.1-66.6
	Low social support in pregnancy				**Not low social support in pregnancy**			
	Cases	**Fetus-years**	**CI or IR**	**95% CI**	**Cases**	**Fetus-years**	**CI or IR**	**95% CI**
Pregnancy loss	2	33.5	1.5	1.5-23.9	13	77.7	16.7	9.7-28.8
Stillbirth	16	110.9	14.4	8.8-23.6	16	227.1	7.0	4.3-11.5
Late stillbirth	21	189.0	11.1	7.2-17.0	26	353.5	7.4	5.0-10.8

Preterm birth	332	386.1	85.9	77.2-95.8	448	713.2	62.8	57.3-68.9
Low birthweight	20	883	2.3	1.5-3.5	40	1744	2.3	1.6-3.1
Small-for-gestational age	88	881	9.9	8.2-12.2	175	1746	10.2	8.7-11.5
Neonatal death	24	114.9	20.9	14.0-31.2	39	191.9	20.3	14.8-27.8
Any adverse perinatal outcome (n=625)[1]	79	96.3	82.0	65.8-102.3	122	214.4	56.9	47.7-67.9
Any adverse perinatal outcome (n=4153)[2]	363	478.4	75.9	68.5-84.1	501	876.7	57.1	52.3-62.4
	IPV in pregnancy				**No IPV in pregnancy**			
	Cases	**Fetus-years**	**CI or IR**	**95% CI**	**Cases**	**Fetus-years**	**CI or IR**	**95% CI**
Pregnancy loss	1	9.0	11.1	1.6-78.9	14	102.3	13.7	8.1-23.11
Stillbirth	3	26.9	11.1	3.6-34.5	29	310.9	9.3	6.5-13.4
Late stillbirth	4	42.9	9.3	3.5-24.8	43	498.8	8.6	6.4-11.6
Preterm birth	48	86.7	55.4	41.7-73.5	730	1011.3	72.2	67.1-77.6
Low birthweight	4	224	1.8	0.7-4.7	56	2401	2.3	1.8-3.0
Small-for-gestational age	20	225	8.9	5.8-13.4	243	2400	10.1	8.9-11.4
Neonatal death	3*	23.9	12.5	4.0-38.8	60	282.4	21.2	16.5-27.4
Any adverse perinatal outcome (n=625)[1]	13	23.8	54.7	31.7-94.1	188	286.9	65.5	56.8-75.6
Any adverse perinatal outcome (n=4153)[2]	55	107.5	51.2	39.3-66.6	807	1246.1	64.8	60.4-69.4

*CESD-10 score was re-scaled to reflect a 10-unit change in score
[1]Any adverse perinatal outcome: miscarriage, stillbirth, preterm birth, low birthweight, small for gestational age, or neonatal death; among those enrolled <20 weeks and with birthweight data
[2]Any adverse perinatal outcome: miscarriage, stillbirth, preterm birth, or neonatal death; among all pregnancies
IR: Incidence rate per 100 fetus-years
CI: Cumulative incidence per 100 pregnancies
PY: person-years
Mild-SD: Mild-to-severe depressive symptoms
MSD: Moderate-to-severe depressive symptoms
LSS: Low social support
IPV: Intimate partner violence

Chapter 7: Discussion

Discussion:
Perinatal depression and adverse infant outcomes among Kenyan mother-infant pairs

The work included in this dissertation is the first of its kind to consider perinatal depression and related psychosocial factors as determinants of multiple adverse perinatal outcomes among Kenyan mother-infant pairs, and it generally contributes to a better understanding of these linkages. We have leveraged data from two large cohorts of Kenyan pregnant women (one cohort among women living with HIV, the other cohort at high risk for HIV acquisition) prospectively into postpartum (to 24 months and 9 months postpartum, respectively) to elucidate connections between maternal mental health and pregnancy and neonatal outcomes. This dissertation utilized a range of methods -- diagnostic performance of psychosocial screening tools (receiver operating characteristic curves), data-driven trajectory modelling (group-based trajectory modelling), longitudinal analyses accounting for autocorrelation and individual-level clustering (generalized estimating equations), and measures of population-level impact (population attributable risk percentages) – many which had not yet been applied in this population to understand maternal mental health and its consequences. Multiple validated psychosocial scales were collected among study participants, allowing us to rigorously assess the burden and relationships between complex factors of depressive symptoms, psychosocial support, and intimate partner violence.

Overall, analyses included in this dissertation consistently highlight that the frequency of perinatal depression is high (~9%-25%) and that low social support and intimate partner violence strongly impact perinatal depression. We identified multiple groups defined by their longitudinal depressive symptoms, about a third of which would benefit from mental health services available within MCH or PMTCT services. Psychological interventions could expand the strengths of existing maternal child health services and PMTCT programs to increase access to mental health screening and treatment of common maternal mental health issues, which could ultimately improve linked maternal-infant health outcomes.

Interpretation of findings on perinatal mental health and dyadic outcomes

Our analyses in Chapters 2-6 are generally mutually supportive and highlight the clear urgency of addressing maternal mental health in Kenya and sub-Saharan Africa more broadly to improve maternal and child well-being. Our findings are generally consistent across data sources, research questions, study populations, and analytic approaches, which strengthens the evidence-base generated by these research findings. This body of work contributes novel, rigorously-obtained epidemiological findings to support the current momentum in Kenya and other East African and sub-Saharan African settings toward systematically offering mental health services to perinatal women. Future studies are urgently needed to explore the pathways of perinatal mental disorder, as well as the mechanisms linking maternal mental health and ensuing adverse pregnancy and infant outcomes to inform more effective interventions. Additionally, studies are needed to comprehensively assess perinatal mental health outcomes that are comorbid with depression, including anxiety and post-traumatic stress disorder in SSA. Analyses that illuminate relationships between perinatal mental health and later infant-child-adolescent outcomes are also needed to fully understand the consequences of maternal distress among African mother-child pairs. Further, implementation science studies are needed to identify the most efficient and effective approaches to improving access to perinatal depression screening and treatment approaches in well-attended clinical settings such as MCH and PMTCT in SSA.

Future directions for integration of perinatal mental health services in MCH and PMTCT

In settings with low-resources for mental health, the World Health Organization (WHO) recommends psychological screening and treatment by non-specialist health providers that is embedded in existing care platforms.[99] Currently available depression interventions globally act across multiple levels of influence (e.g., individual-level, relationship-level, societal-level) and underlying mechanism (e.g., biological, social, somatic) with varying impact. Pharmacological interventions comprise one category, yet guidelines for treatment with antidepressants in

pregnant and breastfeeding women are hindered by a dearth of experimental studies within this population.[10,12,13] Effective psychological interventions including cognitive behavioral therapy (CBT)[8,14–16] and interpersonal psychotherapy (IPT)[8,15,17] are used with high impact to alleviate depressive symptoms in pregnancy and postpartum. Other interventions act psychosocially to increase social support through peer groups and focused attention from clinicians.[14,18,19] Contemporary approaches stimulate somatic responses through physical body behaviors (e.g., exercise, acupuncture) to reduce depressive symptoms.[15,20,21] Existing interventions to alleviate peripartum depression vary in overall efficacy and real-world effectiveness based on factors such as individual or group administration, intention as prevention or treatment, and timing of administration and effect across the peripartum period.

Despite compelling evidence from high-income settings for the effectiveness of pharmacological[8,12], psychological[8,15,55], and psychosocial[8,15,55] interventions to reduce peripartum depressive symptoms, few LMICs have sufficient mental health services and professionals, thus childbearing and breastfeeding women in these settings rarely access such treatments.[56–58] A recent situational report from five countries in SSA reported no dedicated maternal mental health services within district-level facilities.[63] As such, the state of the evidence for implementing available, effective treatments for peripartum depression within the African region is poor.[64–68]

The WHO includes antidepressant medications on the essential medicines list[54], however current WHO mhGAP guidelines[76] state that such medications should only be administered by a mental health specialist, making treatment with antidepressants unlikely for pregnant and breastfeeding women in SSA. This, combined with the reticence among some clinicians to prescribe antidepressants to peripartum women due to potential risks of infant adverse effects makes it nearly impossible.[40,63] Further, acceptability and desirability of antidepressants during this period among African populations are largely unexplored.[63] The few existing studies examining preferences for depression treatment identify conflicting views between different groups in Africa.[77–79]

Few studies have implemented and evaluated mental health treatments generally in SSA[57,69], and particularly within perinatal African women.[64–68] Four studies in SSA reported benefits of psychosocial and psychological treatments for postpartum depression[70–73], yet there is an absence of studies reporting impact of treatments for pregnant women or pharmacological interventions overall in Africa. All four studies were conducted in South Africa by one research team, and were included in four systematic reviews about peripartum depression interventions in LMICs. [67,68,74,75] In settings where specialist clinicians are lacking, "task-shifting" or "task-sharing" of health procedures conventionally handled by highly trained professionals to lower-level cadres or community members is frequently suggested as a burden-reducing and cost-effective approach.[80] Within the global mental health context[76], including peripartum depression in SSA[75,81], task-shifting is increasingly proposed – specifically for lower-level health worker cadres, community health workers (CHWs), peers, or even family members to carry out psychotherapeutic interventions[68,74,75,82]. All four of the psychosocial and psychological peripartum depression interventions with impact in Africa involved task-shifted mental health service provision by lay peer mentors.[70–73]

Overall, the evidence-base for peripartum depression interventions in SSA is thin but studies from the last 10 years in South Africa and a few other non-African LMICs offer encouraging insights. Future intervention trials to address peripartum depression among African perinatal populations should replicate impactful combination psychosocial and psychological interventions which deliver evidence-based, culturally-adapted psychological therapies (e.g., CBT, IPT, problem-solving) via task-shifted care (facility-, community-, or home-based). Such studies should be prioritized for integration into routine MCH services[65,93] in LMICs of Africa to reduce the burden of maternal mental health, prevent adverse mother-infant health outcomes, and ultimately alleviate persisting and disproportionately high mother-infant morbidity and mortality in Africa.

Conclusion

In this dissertation, we show the results from two different studies examining links between perinatal depression over time, other psychosocial factors, and linkages with adverse perinatal outcomes (Chapters 2-6). The four depressive symptom scales we compared (PHQ-2-PHQ-9, CESD-10, EPDS) all performed well in a variety of performance evaluations and should be implemented in care settings to increase perinatal depression ascertainment. Pregnant and postpartum African women are at high risk of depressive symptoms, and our work highlights low psychosocial support and intimate partner violence as the strongest contributing factors to maternal mental health over time. We found that depression in pregnancy puts women at higher risk of pregnancy loss, preterm birth, and low birthweight. Further, low social support was associated with higher incidence of stillbirth.

Overall, it is necessary to integrate mental health screening, treatment, and referral services, particularly interventions that improve social support, within the context of MCH and PMTCT care delivery to improve well-being of mothers and their infants in SSA. A few research groups in SSA have successfully integrated mental health services into MCH care settings. Future efforts to address perinatal mental health and associated consequences should build on this work to test new models for mental health-MCH integration. As momentum builds to implement and expand mental health services in Africa – particularly for pregnant women and mothers – we anticipate dramatic advances in screening and treatment approaches that improve well-being among mothers and infants. This dissertation work contributes substantially to fields of global mental health and maternal child health and identifies critical opportunities to leverage well-attended MCH visits as a platform to deliver non-specialist mental health support to ultimately improve dyadic wellbeing of women and their children.

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VITA

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