Associations between maternal mental health and early child wheezing in a South African birth cohort

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Part 0: Preamble

Declaration

I, *Rae MacGinty*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Signature: Signature Removed

Date: 15 August 2017

Dedication

I would like to dedicate this thesis to my family – Mark, Dorothy, Sean, Carolina and Hannah – for all the love, support and encouragement they have given me over the years and throughout this process. Most of all, this is for my beautiful fiancée Katie without whom I would not be in this position. Thank you for always being there for me, wanting to help no matter the situation and pushing me to follow my dreams (and enrol in the MPH programme in the first place). I hope I can do the same for you in the future, and help you achieve your dreams. You truly are special. I love you.

Thesis Abstract

Background: Wheezing is one of the most common respiratory illnesses in children worldwide. Severe wheeze can result in significant morbidity, caregiver burden and increased health care costs. In addition, early childhood wheeze may be associated with reduced lung function, diminished airway responsiveness, increased risk of asthma in late childhood and subsequent respiratory disease including asthma in adulthood. This is particularly true in those experiencing recurrent wheeze episodes, which in the presence of viral respiratory tract infections, are believed to lead to asthma diagnosis. Thus, it is imperative to understand the risk factors for early childhood wheeze to reduce the increasing burden of respiratory illness.

Recent research has seen a shift to maternal psychosocial risk factors and the impact these have on child respiratory health outcomes, such as wheeze. Various studies, largely conducted in High Income Countries (HIC), have found associations between antenatal or postnatal psychosocial risk factors, such as depression, psychological distress, and Intimate Partner Violence (IPV), and child wheeze and/or asthma diagnosis in early stages of life. However, these studies predominantly considered those in low-income urban regions that were predisposed to respiratory illnesses, including wheeze and asthma.

Utilising the techniques and knowledge gained from previous studies, this research considers the relationship between antenatal or postnatal maternal psychosocial exposures and the onset and recurrence of child wheeze in a South African setting. In the study population used for this research, the reported prevalence of antenatal psychological distress and depression was 23% and 20%, respectively, while 34% of the women were exposed to antenatal IPV. Often those

suffering from poor mental health in these contexts are not recognised and therefore remain untreated. In addition, service provision in these settings is also generally poor. The combination of low levels of social and psychiatric support, with unique political and socio-economic risk factors, may result in more persistent and severe forms of psychosocial exposure in Low Middle Income Countries (LMIC). Given the high prevalence of psychosocial risk factors, as well as the high prevalence of child wheeze, South Africa provides an excellent platform to investigate the association between maternal antenatal or postnatal psychosocial exposure and the development and recurrence of child wheeze in an LMIC context.

Methods: The data used for this research was provided by the Drakenstein Child Health Study (DCHS), a prospective birth cohort study conducted in the Drakenstein region, a peri-urban region outside of Paarl in the Western Cape of South Africa. Pregnant women over 18 years old, between 20-28 weeks' gestation, living in the region were enrolled in a parent study, in order to investigate the epidemiology and aetiology of respiratory illnesses in children. The parent study considered various risk factors, including psychosocial risk factors such as maternal depression, psychological distress and IPV, which were measured antenatally and postnatally by validated questionnaires.

In the context of this research, wheeze was considered to be present if it was identified during any routine study follow-up visit, as well as at an unscheduled lower respiratory tract infection (LRTI) episode visit during the first two years of life. Recurrent wheeze was defined as experiencing two or more episodes of wheeze in a 12-month period. Logistic regression was

used to investigate the relationship between antenatal and postnatal psychosocial risk factors and child wheeze.

Results: From the results, postnatal psychological distress and IPV were associated with experiencing at least one episode of child wheeze (adjusted OR = 2.10, 95% CI: 1.16-3.79 and 1.60, 95% CI: 1.11-2.29 respectively) and recurrent wheeze (adjusted OR = 2.33, 95% CI: 1.09-4.95 and 2.22, 95% CI: 1.35-3.63 respectively), within the first two years of life. No associations were found between antenatal psychosocial risk factors and child wheeze. Of clinical covariates explored, maternal smoking and household smoke exposure, birth weight, gestational age, sex and population group were associated with the presence of wheeze. All of these clinical covariates, as well as alcohol consumption were associated with recurrent child wheeze.

Conclusion: Maternal postnatal psychological distress and postnatal IPV had the strongest impact on predicting wheeze outcomes. These findings suggest that screening and treatment programs which address maternal postnatal psychosocial risk factors may lessen the burden of childhood wheeze in LMIC settings.

Acknowledgements

I would like to express gratitude to everyone who participated in and contributed to the following research. In particular, I thank my supervisor Dr. Maia Lesosky who provided crucial guidance, feedback and support for the duration of this process. Her experience and expertise in biostatistics were critical to this research, and her patience and motivation ensured my success.

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Professors Heather Zar and Dan Stein were essential co-advisors and provided unique knowledge and applications to my research. Heather's comments and advice on child wheeze and respiratory illness and Dan's oversight of psychosocial data were imperative in developing this thesis. Thank you for the guidance and support.

As a member of the Drakenstein study team, I also owe my colleagues and co-workers, as well as the participants of the study, acknowledgement for their contributions. In particular, I would like to thank Polite Nduru, who informally advised me when needed and who graciously acted as a sounding board for new ideas and discussion.

And finally, I would like to extend a huge thank you to the editor- extraordinaire, Katie Florian, for all the late-night edits. Your grammatical knowledge is unparalleled. Thank you for all your patience and support during this process.

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A. Protocol

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Part A: Protocol

1. Introduction:

One of the most pervasive illnesses among children, wheeze contributes to a multitude of health, economic and social issues that affect individuals, families and health systems across the globe. The proposed research seeks to further understand risk factors associated with the onset and recurrence of wheeze by investigating whether maternal antenatal or postnatal psychosocial risk factors predicts child wheezing in the first two years of life in a South African context.

2. Background:

At six years of age, 50% of children have experienced at least one episode of wheezing[1]. Dependent on severity, wheezing episodes can result in significant morbidity, caregiver burden and high health care costs[2]. Furthermore, early childhood wheeze is believed to be associated with reduced lung function, diminished airway responsiveness, increased risk of asthma in late childhood, and subsequent respiratory illnesses including asthma in adulthood[3, 4]. An indication of the severity of respiratory illness within South Africa can be illustrated by asthma-related deaths comparative to the world, as the country is ranked fourth in asthma mortality in the 5-34-year-old age group and fifth for asthma case fatality rates with an estimated 18.5 deaths per 100,000 asthmatics[5, 6].

In an attempt to understand risk factors associated with asthma and childhood wheeze, recent investigative approaches have included an increased focus on how environmental factors, such as psychosocial stressors, may alter immune development and impact child respiratory health[7].

Common mental disorders, including depression, anxiety and psychological distress significantly contribute to the burden of disease and disability in LMIC[8], and comprise up to 10 % of the total global burden of disease[9]. The prevalence of psychosocial risk factors, such as depression and psychological distress, is roughly double in women of childbearing-age compared to men[10]. Increased prevalence of maternal mental health issues, often in the context of lower levels of social and psychiatric support, combined with unique social, political and economic risk factors that women in these settings face, may differentially impact child wheeze outcomes in LMIC relative to HIC. Critically, women who suffer from psychosocial stressors are also more likely to smoke or drink alcohol, which are significant risk factors for child health, particularly in utero[11].

Maternal psychosocial risk factors have been found to negatively affect child health. According to the literature, there is significant evidence suggesting that physical outcomes, such as low birth weight and prematurity, and child developmental outcomes, such as delayed cognitive development, are associated with maternal psychosocial risk factors. These risk factors may contribute to increased prevalence of respiratory illness in those same children. Research has investigated both maternal depression and distress linked to higher rates of asthma and wheeze in early childhood[12-20]. However, the majority of these studies were conducted in HIC settings or included methodological limitations such as small sample sizes. LMIC settings, such as South Africa, may include a unique set of risk factors for antenatal or postnatal maternal mental health and child health outcomes. Better understanding of the linkages may help to improve the care needed to reduce the burden of maternal mental disorders on both the mother and infant. The aim of this study is to investigate the association between maternal antenatal or postnatal psychosocial factors with wheeze in children through 2 years of age in a South African context.

Antenatal versus postnatal psychosocial risk factors

The timing of maternal depression, psychological distress or IPV exposure, whether during pregnancy or postnatally can affect the child differently. The antenatal stage of pregnancy is characterised by physiological and mental transitions that women experience when anticipating and preparing to give birth. For some women, fear and stress relating to pregnancy, coupled with hormonal changes, can be overwhelming[21]. Especially for first-time mothers, warning signs of antenatal depression and psychological distress can go unnoticed, and combined with certain risk factors, such as financial instability or low social support, these mental disorders can become dangerous or detrimental to both mother and child, affecting self-care in pregnant women and birth outcomes for the child[21]. Women who are exposed to depressive symptoms, psychological distress or IPV during pregnancy are also more likely to engage in smoking and alcohol consumption habits, which has a detrimental effect on foetal development. This evidence highlights the importance of early identification or effective screening programs during antenatal care, particularly for high-risk women.

The onset of postnatal depression can be as early as a week after giving birth or months later, and its duration can span from several months to a year. The length of time that a mother suffers without treatment has serious implications on the mother-infant relationship, as it can be difficult to form crucial early bonds[22]. Mothers with depression, as well as psychological distress or IPV exposure, often show less affection toward their children, which can affect their response to infant cues, such as crying. Furthermore, these children show more behaviours linked to stress,

as well as higher cortisol levels, compared to infants whose mothers are not exposed to psychological distress[17, 23]. In LMIC, risk factors of maternal mental health are exacerbated. Lower levels of education, higher levels of poverty, more exposure to traumatic and violent life events, and lower quality maternal mental and physical health care provision compound an already dire situation. Compared to well-resourced areas, women often do not receive the medical or social support they need to combat depression or psychological distress during or after pregnancy. Important to note, however, is that in all contexts – both HIC and LMIC – mental health is not a priority and often receives far fewer resources and attention than clinical care. A specific goal of the current study is to compare the effect of antenatal versus postnatal psychosocial exposures to help elucidate whether these differentially affect wheeze. This will allow informed targeted screening and prevention efforts.

Consequences and effects of maternal psychosocial risk factors on child wheeze

Literature suggests that antenatal maternal anxiety, depression, psychological distress, trauma and IPV exposure have been associated with poor physical infant development and birth outcomes, such as premature birth and low birth weight[24, 25]. These outcomes have adverse effects on the child in various stages of development, as it has been found that infants born prematurely or with low birth weights are at greater risk for weaker immune responses, and thus more prone to various illnesses, such as respiratory illness[26]. Maternal exposure to stress or depression antenatally has been found to increase the likelihood of nutritional deficiencies during pregnancy, as blood flow to the foetus is reduced through increased cortisol excretion, altering maternal IgE and endocrine levels. This, in turn, results in compromised infant immunity[27, 28].

Pregnant women suffering from depression, anxiety, trauma and stress are also more likely to engage in unhealthy behaviours such as alcohol consumption and smoking, which has detrimental effects on foetal development[11].

Maternal postnatal distress has been linked to childhood respiratory illness; in a study based in the United States of America (USA), parental distress increased the risk of wheeze and asthma from infancy through school-age in genetically at-risk children[29]. A weak, developing immune system that interacts with harmful environmental factors such as allergens and cigarette smoke, coupled with poor nutrition, has been found to increase risk of developing asthma in childhood[29-35]. The URECA (Urban Environment and Childhood Asthma) birth cohort study based in low-income areas in the USA also found a strong association between postnatal depression and/or stress with recurrent child wheeze at 3 years of age[12].

Several more studies have found a link between postnatal depression and infant wheezing. A Puerto Rican study found maternal depression was associated with asthma in children at 3 years of age[18], and various studies conducted in Canada have discovered an existing association. Kozyrskyj *et al*. (2008) found that prolonged maternal postnatal distress or depression, through age 7 was associated with an increased risk of asthma[17]. Similar results were obtained in another Canadian study, where persistent maternal postpartum depression increased a child's risk of wheeze at age 6-8 by a factor of 1.5, independent of sex, maternal asthma, low socio-economic status, and low birth weight among others[16]. Further, Alton *et al.* (2015), found an association between postnatal depression and wheeze in pre-school girls[36]. Maternal exposure to IPV was also found to have a significant impact on the onset of child wheeze[37]. Suglia *et al* (2009) found

that the children of those exposed to IPV postnatally, had a two-fold increased relative risk of being diagnosed with asthma, compared to those whose mothers were not exposed[37].

Although significant associations between maternal psychosocial risk factors and child wheeze have been found, the lack of research in an LMIC context warrants an investigation in such a setting, given the high prevalence rates of psychosocial exposures and child respiratory illnesses, and cultural factors and genetic differences in LMIC populations compared to those in HICs. Utilising longitudinal data in a South African low-resourced setting is necessary to better understand the unique constellation of risk factors in these contexts, where the burden of both psychosocial risk factors and respiratory illness outcomes are high. The development of this understanding may be generalizable to other LMIC around the world. Further, given the large burden of disease linked to childhood wheeze and asthma, maternal mental health represents a potential modifiable risk factor to decrease this burden. Mental health services in LMIC are often under-resourced. Therefore, strengthening the research base linking maternal mental health with these common childhood respiratory illnesses may provide critical support for improving screening services and care.

3. Aims & Objectives:

Aim: To investigate the association between antenatal or postnatal psychosocial risk factors and child wheeze through 2 years of age in a South African birth cohort study

4. Methods:

4.1 Setting: The parent study, Drakenstein Child Health Study (DCHS), is a birth cohort study investigating the epidemiology and aetiology of childhood respiratory illness and the determinants of child health in a peri-urban area in South Africa[38]. Located in Paarl, outside of Cape Town, with a population of approximately 200,000[39]. The community, which generally consists of those in low-income households, is stable, with low levels of immigration or emigration. In addition, more than 90% of the local population access health care in the public sector including antenatal and child health services[38]. Further, this area has a well-established, free primary health care system.

4.2 Participants: Participants will include those enrolled in the DCHS, utilising that study's inclusion and exclusion criteria. Those enrolled included pregnant women (20-28 weeks' gestation) 18 years or older, who attended one of two local primary health clinics in the Drakenstein region and intended to remain in this area for at least one year[40]. Inclusion criteria were broad for the parent study to ensure generalisability of results.

4.3 Design: Pregnant women attending one of two primary health care clinics located in the Drakenstein region were recruited into the parent study. These health clinics included: TC Newman, which predominantly serves a mixed-ethnicity population and Mbekweni, which serves a Black-African population[39]. Consenting women completed study questionnaires at scheduled study follow-up visits. Antenatal and postnatal follow-up visits occur at primary health care clinics. Child clinical and respiratory symptoms were completed at each of the study

visits, which occurred at birth, 6-10 and 14 weeks and 6, 12 18 and 24 months post-delivery at primary healthcare clinics. Psychosocial data was collected from mothers antenatally (28-32 weeks' gestation), at 6-10 weeks and 6, 12 18, 24 months' post-partum. All the study measures and time-points used for the collection of data can be seen in Figure A-1 below.

4.4 Measures: The primary outcome of this study will be child wheeze through 2 years of life. This will be measured through maternal report of child wheeze and severity of wheeze at each of the study visits, as well as episodes identified through the active surveillance for respiratory symptoms conducted by the parent study. All risk factor and outcome data in the DCHS is collected longitudinally. Some of these risk factors and potential confounders will be included in the analyses, specifically child feeding practices (breastfeeding versus formulas); HIV status; maternal smoking habits and environmental tobacco smoke (ETS); alcohol consumption; maternal or family history of asthma; birth characteristics, such as gestational age and birth weight; childcare practices; household income; maternal education; socioeconomic status (SES) based on a composite score considering four socio-economic variables: level of education, employment status, household income, and number of assets; and maternal mental health, such as depression, psychological distress, Post-Traumatic Stress Disorder (PTSD), maternal childhood trauma and Intimate Partner Violence (IPV). This study will utilise data collected as part of the DCHS; all the measures listed below are currently administered as part of the parent study and have been approved by the UCT Human Research Ethics Committee (HREC).

Maternal measures will be collected on physical and mental health and socio-demographics. Specific HREC approved measures will include:

1. Socio-demographic variables – including socio-economic status (SES) – household factors and maternal demographics will be collected using an interviewer-administered questionnaire adapted from the South African Stress and Health Study[41].
2. The Edinburgh Postnatal Depression Scale (EPDS) will be used to assess the presence and severity of depression in the enrolled women. This measure is commonly used and is a reliable measure for screening for depressive symptoms[42].
3. The Self- Reporting Questionnaire (SRQ 20) is an instrument designed by the World Health Organization that is used to screen for psychiatric disturbances in an individual[43]. This instrument has been widely validated both internationally and in South Africa[44, 45].
4. The Alcohol, Smoking and Substance Involvement Screening Test[46] is a tool that was developed by the WHO to detect and manage substance use among people attending primary health care services[47].
5. The Intimate Partner Violence (IPV) Questionnaire was adapted from the WHO multi-country study[48] and the Women's Health Study in Zimbabwe[49].
6. The Childhood Trauma Questionnaire Short Form will assess maternal abuse and neglect experienced as a child[50].
7. The Modified PTSD (Post-Traumatic Stress Disorder) Symptom Scale (MPSS) will be used to measure the frequency and severity of maternal PTSD.

Child measures which will be used, and are already approved as part of DCHS, will include:

1. Child health measures – longitudinal data is collected on nutritional outcomes, growth, child feeding (breastfeeding versus formula use), child illness and respiratory symptoms.
2. Vaccination questionnaire - data on child vaccinations is collected.

3. Multiple study questionnaires assess wheeze. The core study child respiratory questionnaire, administered at each scheduled follow-up study visit, seeks to identify wheeze incidence and severity through maternal report. In addition, child wheezing can be identified during an unscheduled lower respiratory tract infection (LRTI) episode visit, or by a combination of maternal and/or study nurse report. For the purpose of this study we will focus on number of reported episodes in the first 2 years of a child's life. This will use a composite count of wheeze episodes based on the described instruments. Specific outcomes linked to this will be a) no wheeze b) ever wheezed and c) recurrent wheeze, defined as 2 or more episodes within a 12-month period.

A graphic illustrating the study measures and the time points for data collection can be seen below:

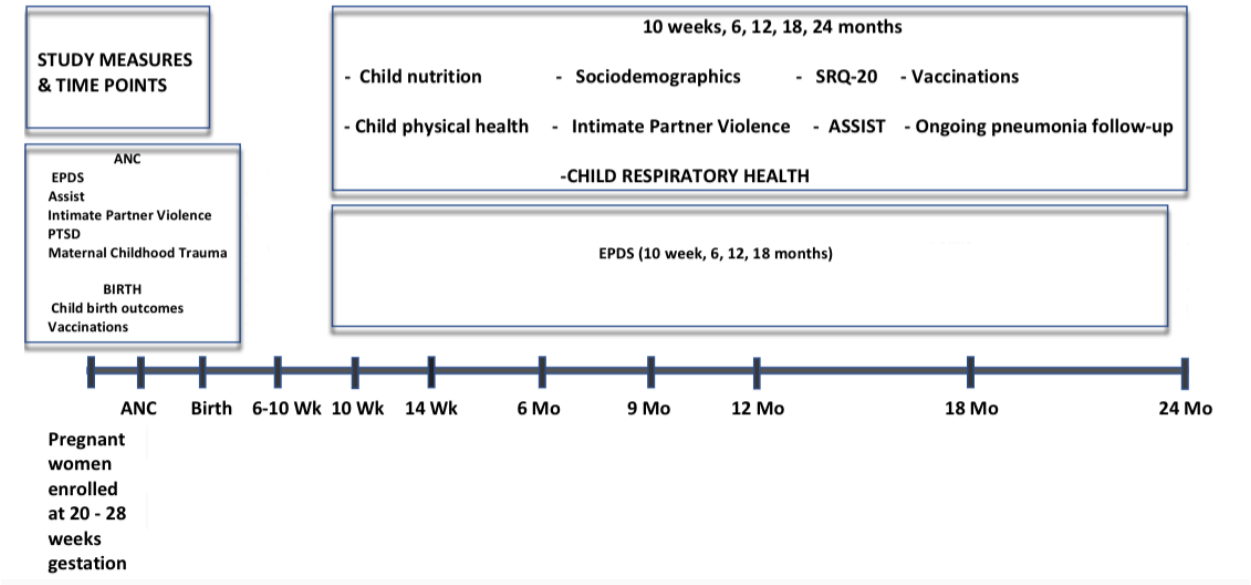

Figure A- 1: Study measures and time points for data collection

The completion of the assessments and questionnaires are overseen by trained study staff, including clinicians, postgraduate students in the health sciences field, clinical and research nurses. These individuals are also provided with the relevant information to refer participants appropriately where necessary.

5. Ethical Considerations:

The DCHS was approved by the Faculty of Health Sciences, Human Research Ethics Committee (HREC), University of Cape Town (401/2009) and by the Western Cape Provincial Health Research committee. In addition, the current study was approved by HREC (Ref number: 387/2017), the acceptance letter can be seen in appendix 1.

Informed consent was obtained in writing from the mothers at enrolment. Participants are not coerced or influenced in any way to obtain consent; all consent is completely voluntary, and consent is renewed annually.

Informed consent is provided in one of three languages, depending on maternal preference. These include: English, Afrikaans or isiXhosa. Trained study staff are present to assist the participants in completing the informed consent forms in the preferred language. Informed consent forms describe the scope and aims of the study, including potential harm or benefits. Potential benefits from study participation include identifying mental or physical health issues and referral to care. Referrals are made for both mothers and children involved in this research; referrals are done by trained staff linked to services in the Paarl area specialising in the issue

identified. Furthermore, all women involved in the study, independent of identified mental or physical health issues, receive information from service providers in the area.

Potential risks include issues of confidentiality and discomfort given the potentially sensitive and upsetting information being recorded. Multiple steps will be taken to minimise these risks: participants are informed that they may withdraw at any time from the study or choose not to take part in certain aspects and that this will not affect the care they receive nor participation in other aspects of the study. Interviews are conducted privately, and participants are assigned a study identification number, and the names of the participants are kept confidential. As a result, direct identifiers are removed from the data collected. All information is stored in a locked filing system at the study sites and/or with the data management team. All data recorded in a storage system is password protected and only those recording and monitoring the data are granted access to the information. Though there are potential benefits and risks, we feel that the risks are minor and the benefits for children and mothers involved in this research justify the study.

6. Statistical Analysis:

All the analyses will be conducted with STATA version 13.0 (College Station, Texas, USA). Descriptive data will be presented as medians and proportions, as appropriate. Mann-Whitney rank sum and Kruskal-Wallis tests will be used to test for associations between categorical and continuous variables, as all continuous variables are nonparametric. Pearson Chi-square test or Fisher Exact tests will also be used to determine if significant associations exist between categorical variables.

Multivariable logistic regression will be used to model the effects of maternal psychosocial risk, both antenatally and postnatally, on the occurrence and recurrence of child wheezing, adjusting for confounding clinical covariates.

Multicollinearity will also be investigated among the psychological risk factors, as well as the measures over time. Two binary response variables will be considered. The first will consider whether a child experienced at least one episode of wheeze, and the second will consider whether recurrent wheeze episodes were present. Recurrent wheeze was defined as two or more episodes in a 12-month period.

7. Proposed Thesis Format & Timeline

The format of the thesis will be as follows:

- Three sections (Part A, B and C) consisting of this protocol, the literature review and the manuscript.
- The literature review (Part B) will consist of a background section, a review of the literature section, a search strategy, and a section considering the 'future needs' for research into the association between maternal psychosocial exposure and child wheeze
- The manuscript (Part C) will consist of a brief introduction section, a methodology section, results, discussion and conclusion:

- The results section will be divided into four sections:
    1. *The effects of antenatal psychosocial exposure on a child experiencing at least one episode of wheeze.* This section will contain the model building process, the final models with interpretation.
    2. *The effects of antenatal psychosocial exposure on child recurrent wheezing episodes.* This section will contain the model building process, the final models with interpretation, and a model checking section to verify the model.
    3. *The effects of postnatal psychosocial exposure on a child experiencing at least one episode of wheeze.* This section will contain the model building process, the final models with interpretation.
    4. *The effects of postnatal psychosocial exposure on child recurrent wheezing episodes.* This section will contain the model building process, the final models with interpretation, and a model checking section to verify the model.
- The discussion section will detail the effects of the outcome variable on the exposure of interest, linking the findings with the literature. This section will also identify the strengths and limits of the current study.
- The conclusion section that will summarise study findings and implications, as well as contextualisation in the broader field of literature.

Table A-2: Proposed timeline for completing the thesis:

SECTION OF THESIS	MONTH FOR COMPLETION
INTRODUCTION, LITERATURE REVIEW, BACKGROUND, METHODS SECTIONS	End of April
DATA SET FINALISED	May
DESCRIPTIVE STATISTICS & EXPLANATORY ANALYSIS	End of May
BUILDING MODEL, FINALISING MODEL AND CHECKING	June - July
COMPLETING FURTHER WRITTEN SECTIONS, SUCH AS DISCUSSIONS, AND CONCLUSION	End of July
EDITING	End of July – 15 August
SUBMIT THESIS	15 August

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Part B: Structured Literature Review

1. Background:

Recurrent wheeze in early childhood is a well-established symptom and precursor to asthma diagnosis at later stages in life. Recurrent wheeze is the source of significant morbidity in children. In young children, wheeze, especially if severe, can affect quality of life both for the child and family, increasing visits to healthcare facilities and presenting an economic burden to both families and healthcare systems[1, 2].

Critically, early childhood wheeze has been linked to reduced lung function and an increased risk of asthma diagnosis later in life[3, 4]. The most crucial link is the one to asthma, which is the most common chronic illness among children. Though historically asthma has been associated with High-Income Countries (HIC), new evidence suggests that the prevalence of respiratory illness in Low-to-Middle Income Countries (LMIC) has rapidly increased, while plateauing in HIC around the world[5, 6.]

The prevalence and severity of asthma in LMIC has been underestimated, in part due to health systems that are overwhelmed with infectious diseases and other priorities. However, ISAAC, the largest global epidemiological study of asthma prevalence in children, has shown that asthma is as common or more common in African children, compared to global prevalence, and of higher severity[6, 7]. There are many factors unique to LMIC environments that may be driving higher severity of disease; these include lack of diagnosis, limited access to care, affordability of therapy, environmental exposures, genetic susceptibility to more severe disease or a combination of these[6-10]. In a South African context, asthma remains a significant source of morbidity and

mortality; South Africa is ranked fourth in asthma mortality worldwide and fifth for asthma case fatality rates with an estimated 18.5 deaths per 100,000 of those diagnosed with asthma[6, 8, 9].

With rising prevalence of asthma in LMIC settings, understanding risk factors, such as recurrent wheeze, may help reduce the burden of the heterogeneous disease. Evidence has emerged suggesting that infants may be susceptible to wheeze and asthma in utero, through antenatal exposures such as smoke, alcohol and drug use, and hormonal releases that can disrupt foetal development[11-18.] These associations support more recent investigations into how environmental factors, such as psychosocial stressors, may alter immune development and impact child health, including wheeze and, later, asthma[19-28].

The determinants of psychosocial exposures have received wide consideration, as the prevalence of mental illness has rapidly increased in conjunction with ever-expanding societal stressors. Pressures created by gender discrimination and factors, such as poverty and intimate partner violence (IPV) create an environment in which women are at a disadvantage and far more likely to develop depression, anxiety or psychological distress relative to men[29-31]. Furthermore, the prevalence of depression is roughly double in women of childbearing-age compared to men. In HIC, approximately 10% of pregnant women and 13% of women who have recently given birth suffer from psychological distress and depression[32].

A higher prevalence of antenatal and postnatal depression is observed in LMIC, where 15.6% of pregnant women and 19.8% of women who have recently given birth suffer from this condition[32]. Furthermore, approximately 16-50% of women are estimated to suffer from violence

in their lifetime, exacerbating mental deterioration, which can be detrimental to a mother and her child's health[33]. Evidence of high prevalence of psychosocial exposures in LMIC, such as South Africa, can be observed by the study population of Drakenstein Child Health Study (DCHS). In 2015, the reported prevalence of antenatal psychological distress and depression was 23% and 24%, respectively[34]. Almost half of the mothers in the cohort (46%) were exposed to IPV in their lifetime[34]. Often those suffering from poor mental health in these contexts are not recognised and therefore remain untreated. Thus, low levels of social and psychiatric support, combined with unique political and socio-economic risk factors, may result in more persistent and severe forms of psychosocial exposure in LMIC.

The aim of this literature review is to investigate the associations between antenatal and postnatal maternal psychosocial exposure and the onset of child wheeze and/or asthma. The psychosocial stressors include maternal depression and anxiety, and exposure to IPV and traumatic events. This is a critical area of investigation given the twin burden of respiratory illnesses and mental disorders in low-resource settings, such as South Africa.

2. Literature review objectives:

The objectives of this literature review are to summarise literature investigating maternal psychosocial risk factors and child wheeze or asthma; to investigate the extent to which previous literature has compared antenatal and postnatal psychosocial risk factors and their impact on child wheeze and/or asthma; to describe the biological and epigenetic mechanisms associated with antenatal psychological distress, such as depression, anxiety and traumatic event exposure

on foetal development; to describe maternal postnatal psychosocial risk factors and the mechanisms and previously reported impact on child wheeze and/or asthma; to determine the limitations associated with previous studies.

3. Search strategy:

Searches for literature were conducted using PubMed, Google scholar, and the Google search engine. The following phrases and terms were used to navigate the search engines: “psychosocial illness”, “maternal”, “child wheeze”, “child asthma”, “antenatal depression AND child wheeze”, “postnatal depression AND child wheeze”, “maternal psychological distress”, “IPV AND child wheeze”. Additional articles were identified from the reference lists and bibliographies of selected articles and systematic reviews, as well as from personal communication with researchers associated with the DCHS.

The inclusion and exclusion criteria included studies conducted in English. The search was not limited to a particular timeframe. In addition, all study designs were considered; however, particular attention was paid to longitudinal study designs.

In total 27 studies and one systematic review were found, and all were considered in the summary of the literature. However, the main focus of this research was the association of psychosocial exposure with outcomes of wheeze and recurrent wheeze in early childhood; studies that considered asthma diagnosis as an outcome were also considered in the literature review. This was due to limited focus on the association between child wheeze and psychosocial

risk factor exposure in the literature, as well as the similar mechanisms at play when asthma was considered as an outcome. In addition, early childhood wheeze, particularly recurrent wheeze has been linked to asthma diagnosis.

4. Summary of the literature:

4.1 Review of previous studies findings on the association between maternal psychosocial exposures and child wheeze and/or asthma

Most studies examining the association between maternal psychological exposures and wheeze and/or child asthma have been conducted in the United States of America (USA), and the majority of these studies consider those in low socio-economic areas and infants at high risk for asthma. There have been a few retrospective and cross-sectional studies, and although associations were found in these studies, given their cross-sectional methodology, causality cannot be determined[21, 22]. Prospective studies allow the investigator to observe the development of disease, from multiple exposures, over a long period, which is important to establish temporality. As a result of this strength, particular attention was paid to prospective studies to investigate the relationship between maternal psychosocial exposures and the development of child wheeze and/or asthma diagnosis.

4.1.1 Prospective studies investigating the association between maternal psychosocial exposures and child wheeze and/or recurrent wheeze

The URECA (Urban Environment and Childhood Asthma) birth prospective cohort study, like many studies, recruited low socio-economic status and children at high-risk for asthma, and considered antenatal and postnatal depression and/or stress as the primary exposure[24]. A total of 560 pregnant women with family history of allergic rhinitis, asthma and/or eczema and at least 34 weeks of gestation were enrolled in the study[24]. Biomarkers were utilised to measure the immune function of the infant exposed to antenatal and postnatal depression and/or stress, particularly cytokine responses of blood cells at three years of age[24]. With high retention of 85%, the study found a positive association between maternal stress and recurrent wheeze at 3 years of age[24].

Recurrent wheeze, in the URECA study, was defined as at least two episodes of wheezing during the first 3 years of life, with at least one episode during the third year[24]. Various types of stressors related to personal hardships had the strongest relationships with recurrent wheeze. Notably, maternal depression and/or stress was not found to be associated with allergy sensitisation or cytokine responses[24].

In another USA-based study, pregnant mothers from low-income urban communities were enrolled and antenatal and postnatal mental health measures captured, as well as specific wheeze phenotypes and atopy data among children[25]. Antenatal psychological distress was found to have an association with overall wheeze (OR=1.66), transient (birth to 2.5 years) wheeze (OR=2.25),

and persistent (birth to 5 years) wheeze (OR=2.69). No association was found between psychological distress and sensitisation to indoor allergens[25]. The findings from this study, as well as the URECA study, suggest that atopy and asthma have different risk factors. However, other environmental exposures, such as environment tobacco smoke (ETS) exposure, may interact with psychosocial risk factors increasing the risk of wheeze or asthma.

Similar findings were reported by Mathilda Chiu et al (2012), who also recruited the study population from low-income urban communities in the USA. Maternal antenatal and postnatal depression were both captured, and recurrent wheeze was defined as two or more episodes of wheeze during the first two years of life[26]. The study also considered the interaction between prenatal stress and maternal sensitisation, indexed by allergen-specific IgE from maternal serum, to investigate the effects of family history of allergies and onset of child wheeze[26]. A novel aspect of the analysis was the consideration of antenatal and postnatal stress separately, and both were found to have a significant association with recurrent child wheeze[26].

However, when antenatal and postnatal stress were considered together, only mothers with high stress in both periods had an association with recurrent child wheeze (adjusted OR =3.04)[26]. As both antenatal and postnatal depression and/or stress have been found to play vital roles in child health outcomes, they should be taken into consideration, as the two periods are linked. This is particularly true, as antenatal depression has been found to be a precursor and risk factor for postnatal depression[35]. Together antenatal and postnatal maternal stress appears to compound risk producing a much greater effect on child respiratory health.

In addition to these results, Mathilda Chiu et al (2012) found that the strength of association between increased wheeze and antenatal stress was higher in those with non-sensitised mothers compared to those who were sensitised[26]. This finding suggests that maternal mental health may have a significant impact on nonatopic wheeze or asthma. This is of major importance in LMIC as atopy is much less strongly associated with wheeze or asthma in LMIC settings compared to HIC. As this is the case, the predominant phenotype of childhood wheezing or asthma is viral-induced rather than atopic in LMIC[36, 37]. Interestingly, in a cross-sectional study conducted in Latin America, maternal depression was found to have a similar impact on atopic and nonatopic child wheeze[38].

Further research of infants at high risk for asthma in the USA was conducted by Wright et al (2002), who recruited 496 mother-child pairs in a prospective birth-cohort study in Boston, USA. High levels of maternal stress at 2-3 months after birth were associated with an increased risk of recurrent wheeze in children at 14 months of age. The impact of postnatal maternal stress on child wheeze was found to be independent of the mother's smoking habit, breast-feeding, allergen exposure, low birth weight and lower respiratory infections[23]. This, like the other three USA-based studies, suggests that maternal stress may have a direct impact on increased risk of child wheeze.

Alton et al. (2015), who considered the association of postpartum depression and wheeze in pre-school girls, found that there was five times increased risk in child wheezing by age three years, when the mother experienced postnatal depression compared to households with no maternal depression[39].

Most of the longitudinal studies described above were conducted in North America and all had similar strengths and weaknesses. The strengths include the prospective nature of the studies, the high levels of retention and standardised measures during critical periods of development[24]. However, all the studies included low-income, urban, minority families who were at high-risk of asthma. Thus, the results, although important to obtain, may not be generalizable to a broader population within HIC regions nor populations in LMIC. It is important to broaden this research to a LMIC context, given the increased wheeze and asthma burden and the unique set of risk factors and access to healthcare services. Another potential bias could result from maternal recall of wheeze, particularly if not conducted in a prospective setting. Although this is accepted procedure, if not conducted properly, it could lead to potential underreporting, especially if the mother is overwhelmed and less aware of her child's health. Conversely, a mother with higher stress and anxiety may over-report wheeze, which would overestimate the true association between maternal mental health and child wheeze[26]. A further limitation is the heterogeneity in definitions for recurrent wheeze with some studies using 2 or more, others 3 or more, or the time frame in which recurrent wheeze is defined. For example, in the study conducted by Mathilda Chiu et al (2012), recurrent wheeze was defined as two or more episodes over a 24-month period, whereas, Ramratnam et al (2017), defined it as two or more episodes, with at least one episode in the third year of life.

4.1.2 Prospective studies investigating the association between maternal psychosocial exposures and child asthma diagnosis

More severe and persistent maternal anxiety, depression or psychological distress appears to have the greatest effect on child wheeze and asthma diagnosis later in life. A study conducted in Puerto Rico considered the impact of maternal depression on asthma diagnosis when the child was one and three years old respectively. The study found that at one year of age, the severity of asthma, indicated by a greater risk of hospitalisation, was increased in those whose mothers displayed depressive symptoms[40]. This was further evident when the child was three years old, as maternal depression remained a risk factor for asthma diagnosis and hospitalisation due to asthma[40]. This suggests that persistent maternal depression and/or stress has a continued impact on wheezing or asthma through early childhood.

Several studies conducted in Canada confirmed that persistent maternal postpartum depression, increased a child's risk of asthma at age 6-8 years by a factor of 1.5, independent of sex, maternal asthma, low socio-economic status, and low birth weight among others[41]. This also suggests that there could be a direct link between maternal depression and/or stress and child asthma diagnosis.

In response to the consistent genetically high-risk children utilised in the USA-based studies, population-based studies were conducted in Australia, Canada, the UK and the Netherlands. Both the studies in the UK and Netherlands found significant associations with antenatal maternal depression and anxiety, and child asthma at age 7[42, 43]. Meanwhile, the Australian and

Canadian studies found associations between postnatal maternal depression and child asthma at age 6-7 years[27, 28].

The novelty of both the Australian and Canadian population-based studies was the consideration of those with low-risk asthma diagnosis, as both urban and rural settings were included; and thus, true population demographics were considered[27, 28]. Kozyrskyj et al. (2008) found that prolonged maternal distress or depression, through 7 years of age in Canadian urban and rural children, was associated with an increased risk of asthma in a low-risk cohort[28].

One of the main objectives of the Australian study was to investigate whether the increased risk of asthma was only associated with those exposed to more severe depressive symptoms relative to those exposed to lower, subclinical levels of depressive symptoms, which are more common[27]. The study found that persistent and increasing maternal depressive symptoms resulted in a 3-fold increase of child asthma at 6-7 years[27]. Notably, no association was found between low exposure or subclinical depressive symptoms and asthma diagnosis[27]. To confirm the results, and address temporality, a sensitivity analysis was conducted, in which all those who experience at least one episode of wheeze during the first year of life were excluded[27]. In this subset, similar results to the main analysis were obtained, as it was found that persistent and severe maternal depressive symptoms resulted in increased risk of asthma diagnosis in later stages of life[27]. Although, the study was conducted in older children, it is important to note that persistent maternal depression has a continuous effect on child respiratory health outcomes over time.

Women exposed to IPV have also been found to have an association with childhood asthma, as the mothers' ability to care for the child is disrupted[44]. This maternal stressor has been linked to poor maternal-child interactions in early life, which could result in disturbed stress reactivity, compromised self-regulation and disrupted immune development, providing the platform for asthma development[44]. Notably, among children with asthma, difficulties with emotion regulation have been found to increase asthma severity, which supports the existence of a relationship between regulation and asthma[44]. Disrupted stress reactivity may be further exacerbated if children witness violence against their mothers [44].

Maternal exposure to IPV was considered as the primary exposure of interest in relation to childhood asthma diagnosis in the Fragile Families and Child Wellbeing study (n=3116)[44]. IPV exposure was measured at birth, 12 months and 36 months after birth[44]. The study found that if the mother was exposed to IPV at any of the time points, the child had an increased relative risk of asthma diagnosis compared to those where the mother was not exposed to IPV. If the mother was exposed to IPV at both postnatal time points (12 and 36 months), the child had a two-fold increased relative risk of being diagnosed with asthma[44]. Although, the results were significant, there is the potential risk of under-reporting IPV, which would underestimate the true association between maternal IPV and child asthma diagnosis.

4.2 The mechanisms of antenatal and postnatal mental health and their effects on children respiratory health outcomes

Antenatal psychological stress and IPV exposure, which is mediated through the increased activity of the hypothalamic-pituitary axis (HPA), has been identified as a crucial exposure that impacts asthma and allergy susceptibility in the offspring[45, 46]. The HPA is the central stress-response system which is responsible for the secretion of hormones by the hypothalamus and pituitary gland in the brain. These then stimulate the release of cortisol, adrenaline and noradrenaline from the adrenal glands[47]. During pregnancy, these substances can be transmitted to the foetus and can influence its development. This is evident from a study conducted by Bair-Merit et al (2015), which found that children aged 7 and 15 months who were exposed to maternal IPV were cortisol 'reactors' and were at an increased risk of asthma diagnosis compared to those not exposed[46]. Maternal prenatal psychosocial stress has been found to increase the risk of prematurity, low birth weight, offspring neurodevelopmental and cognitive delay, attention-deficit hyperactivity disorder, and other mental health disorders in the offspring[15, 47-50]. These risk factors may also contribute to increased prevalence of respiratory illness in the same children. Furthermore, prenatal maternal stress may influence childhood wheeze through its documented relationship to low birthweight[51]. It has been hypothesised that children with physically smaller airways may be intrinsically at greater risk for wheezing or lower respiratory tract illnesses in early life[23].

Further, maternal stress may affect airway inflammation through influences on the immune system, which could promote airway obstruction[23]. Genetic factors in utero and postnatal

environmental factors, as well as the timing of exposures to these factors, likely play a role in the differentiation of the immune response[23]. Thus, poor maternal psychosocial exposure has the potential to disrupt the development of the immune system during childhood, providing the platform for inflammatory processes and distorted reactivity to environmental exposures which could result in airway obstruction and recurrent wheeze[23].

In addition, evidence suggests that antenatal stress exposure can alter the gut microbiota of the infant, affecting immunological pathways in the infant, which could result in increased susceptibility to wheeze and asthma[52]. Epigenetic changes linked to maternal stress may be another mechanism affecting child lung health; Trump et al. (2016) found that calcium- and Wingless/ Integration-1 (WNT) signalling in infants, needed for lung development in utero, were epigenetically deregulated when exposed to maternal antenatal stress. These epigenetic changes were then linked to wheezing later in the child's life[53].

Postnatal psychological stress may affect child recurrent wheeze through different mechanisms. Potential pathways could stem from nutrition deficiencies, as women suffering from anxiety and depression are less likely to breastfeed, with consequences on infant immune development[54]. Women suffering from mental illness may also be more likely to engage in unhealthy habits such as smoking and drinking. Passive smoke exposure, as well as environmental tobacco smoke (ETS) exposure, are well-known risk factors for respiratory illness and have been shown to have detrimental effects on lung health. Mother-child interactions can also be interrupted when the mother experiences depression, anxiety or IPV. This can affect the mother's ability to provide

appropriate care for the child, providing poor hygiene practices and food supply, which could negatively impact child growth and health[55, 56].

5. Need for further research:

Although a significant association between maternal mental health and child wheeze and/or asthma has been found in the literature, these studies have several limitations. Importantly, there is a dearth of evidence from LMIC contexts, especially Africa. A study conducted in Africa, specifically South Africa, is necessary as there is a rapidly increasing prevalence of wheeze and asthma. According to the World Health Organisation (WHO), there are also higher levels of perinatal depression and stressors in LMIC relative to HIC[33]. Given this double burden, it is therefore critical to investigate LMIC/African contexts.

Further needs in future research, particularly in LMIC, should consider generalizability of the study population. The Drakenstein Child Health Study (DCHS), a longitudinal birth cohort study which enables prospective measurement of the exposure/outcome relationship, provides a study population generalizable to a large proportion of the South African population, and populations in other LMIC regions around the world.

Researching links between psychosocial risk factors and wheeze in LMIC is vitally important to understand the aetiology of wheeze and/or child asthma, as the prevalence of respiratory illness is rising in these regions. Therefore, further research is needed in LMIC, and the Drakenstein study provides a unique platform from which to conduct it.

6. Conclusion:

According to the literature, there is evidence that maternal mental health is associated with increased risk of child wheeze and childhood asthma. However, most of the existing research has been conducted in HIC, and in high-risk and non-generalizable populations. Further study in LMIC contexts, such as South Africa, is needed given the high burden of maternal mental illness and of childhood respiratory illness. As a result, we will better understand the risk factors associated with child and recurrent wheeze, and be more equipped to handle the burden posed by wheeze and asthma diagnosis later in life

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Part C: Manuscript

Associations between maternal mental health and early child wheezing in a South African birth cohort.

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Abstract:

Background: Wheezing in early childhood is common and has been identified in high-income countries (HIC) as associated with maternal antenatal or postnatal psychosocial risk factors. However, the association between maternal mental health and childhood wheezing has not been well studied in low-and-middle-income-countries (LMIC), such as South Africa.

Methods: Pregnant women over 18 years old, between 20-28 weeks' gestation, and attending either of two catchment area clinics were enrolled in a South African parent study, the Drakenstein Child Health Study (DCHS). Psychosocial risk factors including maternal depression, psychological distress, early adversity and intimate partner violence (IPV), were measured antenatally and postnatally by validated questionnaires.

Two outcomes were evaluated: Presence of wheeze (at least one episode of child wheeze during the first 2 years of life); and recurrent wheeze (2 or more episodes of wheezing in a 12-month period). Logistic regression was used to investigate the association between antenatal or postnatal psychosocial risk factors and child wheeze, adjusting for clinical and socio-demographic covariates.

Results: Postnatal psychological distress and IPV were associated with both presence of wheeze (adjusted OR = 2.10, 95% CI: 1.16-3.79 and 1.60, 95% CI: 1.11-2.29 respectively) and recurrent child wheeze (adjusted OR = 2.33, 95% CI: 1.09-4.95 and 2.22, 95% CI: 1.35-3.63 respectively).

Conclusion: Maternal postnatal psychological distress and IPV were associated with wheezing in early childhood. Thus, screening and treatment programs to address maternal psychosocial risk factors may be potential strategies to reduce the burden of childhood wheeze in LMICs.

Key words: *Antenatal, postnatal, maternal depression, psychological distress, Intimate partner violence, wheeze, low and middle income countries*

1. Introduction:

Wheezing in early childhood is very common, with 50% of children from HIC reported to have experienced an episode of wheezing before 6 years of age[1]. Wheezing illness comprises a spectrum of disease, ranging from transient to recurrent, a proportion of which is associated with asthma. Recurrent wheeze has been identified as a risk factor for asthma development[2]. Asthma is the most common chronic illness in children, and particularly high in Africa; thus, it is important to understand the risk factors associated with wheeze onset[2]. There are many causes of wheezing in early childhood and several risk factors associated with the development or severity of wheezing. The most common risk factors include environmental tobacco smoke (ETS) exposure; genetic predisposition; early viral lower respiratory tract infections (LRTI); low socio-economic status and poor living conditions; as well as an increased risk in males[3]. A more recent focus is on maternal psychosocial exposures and the impact these have on child wheeze development and recurrence.

Antenatal or postnatal maternal exposure to psychosocial risk factors have been reported to be associated with development of child wheeze[4-13], but there is sparse data from LMIC. Most research has been conducted in HIC, and predominantly in high-risk populations. These results provide valuable insight into the relationship between maternal mental health and respiratory outcomes in children, but unique genetic and cultural factors may impact associations in LMIC differently than HIC. This study will investigate the association of antenatal and postnatal maternal mental health with child wheeze in South Africa, addressing key gaps in the literature by expanding prior research to a LMIC in a generalizable population.

2. Methods:

2.1 Setting*:* This study was a sub-study of the Drakenstein Child Health Study (DCHS), a multidisciplinary birth cohort investigating the epidemiology and aetiology of childhood respiratory illness and the early life determinants of child health in a peri-urban area in Paarl, South Africa[14]. The catchment population is approximately 200,000, consisting mainly of those with low socio-economic status, who reside in informal settings or crowded conditions[14, 15]. More than 90% of the population access public healthcare services for their primary care[14].

2.2 Participants*:* Participants were those enrolled in the DCHS. Inclusion criteria were women 18 years or older, who were at 20-28 weeks' gestation, attended one of two local clinics, provided informed consent and intended to remain in the area for at least 1 year[16]. Women were followed through childbirth and mother-child pairs were followed through childhood. The current study reports on a follow-up period until children were 2 years of age.

2.3 Design: The birth cohort recruited pregnant women attending one of two primary health care clinics; TC Newman Clinic, which predominantly serves a mixed-ethnicity population and Mbekweni Clinic, which serves a Black-African population[15]. Child clinical and respiratory symptom questionnaires were completed at each of the study visits, which occurred at birth, 6-10 and 14 weeks and 6, 12, 18 and 24 months post-delivery at primary healthcare clinics.

2.4 Measures: Risk factor and outcome data collection is ongoing and recorded longitudinally as part of the DCHS. The primary outcome of this study was child wheeze through 2 years of age.

Wheeze outcomes

Child wheeze was measured through maternal report at each of the study visits, as well as episodes identified through the active surveillance for respiratory symptoms associated with LRTI. Active surveillance was performed by nurses at the primary clinics and assessed in real time[14, 17]. Study nurses were trained in respiratory examination of children, and had to attend frequent competency assessments[17]. Measurements of lower respiratory tract infections (LRTI) included ambulatory and hospitalised pneumonia cases, as defined by World Health Organization (WHO) criteria[14]. As the mothers were interviewed frequently, it was also possible to retrospectively capture respiratory events occurring at other facilities or outside the area[17]. Any information on respiratory events captured outside of the clinics was obtained by review of medical records[17].

Two binary outcome variables were considered: Whether the child experienced at least one episode of wheeze during the first two years of life, or whether the child experienced recurrent wheeze episodes (defined as 2 or more wheeze episodes in a 12-month period). Wheeze was considered present if it was reported during any routine study visit, or identified by study staff members when examining the child at a LRTI visit in the first two years of life.

Maternal psychosocial measures:

Maternal psychosocial data was collected antenatally, and postnatally at 6-10 weeks and 6, 12, 18, 24 months postpartum[15]. A number of validated questionnaires were used to measure psychosocial risk factors: The Edinburgh Postnatal Depression Scale (EPDS) – collected only

through the 18-month visit – is a widely used and reliable measure of depressive symptoms, and was used to measure maternal depression[18]. Each of 10 questions were scored 0-3, and totalled[15]. A cut-off value of 13 was used to separate the participants into above- or below-threshold groups[18, 19].

The Self-Reporting Questionnaire 20-item (SRQ20)[20], a widely used and validated measure, was used to determine the presence of maternal psychological distress[21, 22]. Each item was scored 0-1, and a total score generated[15]. A cut-off value of 8 dichotomised participants into an above- or below-threshold group[15, 21, 23].

The Intimate Partner Violence (IPV) Questionnaire was used to assess maternal physical, emotional and sexual violence exposure[24, 25]. Exposure to IPV was dichotomised by those recently experiencing any one of the three violent exposures versus no exposure.

Other psychosocial measures included: the Childhood Trauma Questionnaire, to assess childhood abuse and neglect[15, 26], which was dichotomised into above- or below-threshold based on any exposure versus no exposure; the Modified Post-Traumatic Stress Disorder Symptom Scale used to screen for current post-traumatic stress disorder (PTSD)[27], which was categorised into three mutually exclusive levels (no exposure, trauma exposed and suspected PTSD) based on experiencing a traumatic event.

Clinical and sociodemographic data:

Covariates considered for the analyses included: child feeding practices; HIV exposure; maternal smoking and environmental tobacco smoke (ETS) exposure, assessed by the number of smokers

in the child's household; alcohol consumption during pregnancy, measured by the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[28]; maternal or family history of asthma ascertained by maternal report; birth characteristics, such as gestational age and birth weight, measured by study staff; child vaccination; socio-economic status (SES) based on a composite score considering four socio-economic variables: level of education, employment status, household income, and number of asset[29]. Standardised scores were divided into quartiles, which included 'low', 'low-moderate', 'high-moderate', and 'high' groups. A time variable, in months, was also generated to measure a child's follow-up time throughout the 24-month period.

2.5 Ethical Considerations: The DCHS was approved by the Faculty of Health Sciences, Human Research Ethics Committee (HREC), University of Cape Town (401/2009) and by the Western Cape Provincial Health Research committee[14]. Mothers provided written informed consent, which was voluntary and renewed annually.

The current study was approved by HREC (Ref number: 387/2017).

2.6 Statistical Analysis: Analyses were conducted with STATA version 13.0 (College Station, Texas, USA). Descriptive data was presented as medians, interquartile ranges (IQR) and frequencies (proportions), as appropriate. Mann-Whitney rank sum and Kruskal-Wallis tests were used to test for associations between categorical and continuous variables, as all continuous variables were nonparametric. Pearson Chi-square test or Fisher Exact tests were used to determine if significant associations existed between categorical variables.

Multivariable logistic regression was used to model the associations of maternal psychosocial risk, both antenatally and postnatally, with the occurrence and recurrence of child wheezing, adjusting for confounding clinical and sociodemographic covariates. As multicollinearity was present among the psychosocial risk factors, they were considered individually in a series of logistic regression models. As the postnatal psychosocial risk factor measures were also found to be correlated over time, we utilised data from the 6-month scheduled visit as a proxy for postnatal exposure, as most wheezing episodes occurred within the first 6 months of life.

Diagnostic checks were generated for all multivariable models. Based on Pearson's chi-squared and/or the Hosmer-Lemeshow test, all the models were found to correctly specify the association between perinatal psychosocial risk factors and wheezing outcomes.

3. Results:

3.1 Descriptive statistics and exploratory analysis

In total, 1137 women with 1143 live births, were considered for this study, Figure C-1. At the end of the 2-year follow-up, 985 children were still active in the study, and the total child follow-up time was 1859.54 years.

Socio-demographics & clinical factors.

The median maternal age was 26 (22.3 – 31.1) years; 22% of the women were HIV-infected, with Mbekweni having a significantly higher proportion (36.6%) of those with HIV compared to TC Newman (3.3%), Table C-1. Approximately 27% of the women smoked during pregnancy, with the majority (53%) from TC Newman, and higher numbers of household smokers were reported by those attending TC Newman relative to Mbekweni. Antenatal alcohol consumption was also significantly higher among those attending TC Newman (15.9%) compared to Mbekweni (6.8%), Table C-1.

Socio-economic status (SES) varied between the two sites, with Mbekweni having a higher proportion of low SES households; overall approximately 87% of participants lived in households that earned less than R5000 (387 USD) a month, Table C-1.

Birth Characteristics.

An even distribution of males and females were born; a small proportion (7%) of births were premature (<37 weeks' gestation). Median birth weight was approximately 3kg. Approximately 90% of the children (n=1023) were breastfed, and 84% of children had received both breast milk and formula feed during the follow-up period, Table C-1. Although not seen in Table C-1, two (0.17%) of the children were HIV positive.

Wheezing episodes

In total, there were 924 wheeze episodes (crude incidence rate = 497 cases per 1000 person-hours of follow-up time) throughout the 24-month follow-up period, most of which occurred in those children attending TC Newman (55%). Mother or care-giver reported wheeze contributed 437 (47.3%) episodes and the remainder (n=484) were reported or identified during the active surveillance, and thus associated with LRTI. As much of the wheezing was associated with LRTI, it was not considered as an individual covariate. In addition, a high proportion of episodes occurred within the first 6 months of life (n=452, 48.9%). At least one episode of wheeze was experienced by 479 (41.9%) children during the 24-month follow-up period, while 186 (16.3%) had recurring wheezing episodes.

Psychosocial risk factors

Antenatal

Antenatal depression was present in 24% of the women (n=237) with similar distribution across sites. In addition, approximately 20% suffered from antenatal psychological distress, with

majority at TC Newman, Table C-2. There was a high prevalence of antenatal IPV in the study, with approximately 34% of participants being recently exposed; this was significantly different between the two sites, with majority at TC Newman. Exposure to maternal childhood trauma was also higher in those attending TC Newman (41%). However, PTSD was more common at Mbekweni than TC Newman, Table C-2.

Postnatal

Psychosocial exposures were captured at multiple scheduled time points postnatally. A relatively consistent level of exposure of maternal depression, psychological distress and IPV existed across the scheduled follow-up visits, Table 2. Based on Chi-Squared Tests of Independence (supplementary Table C-7 - C-10), high levels of correlation existed among the exposures. The prevalence of depression, psychological distress and IPV exposures were greater in those attending TC Newman compared to those attending Mbekweni.

3.2 Univariate and multivariable analysis

3.2.1.1 Antenatal psychosocial risk factors and presence of child wheeze

Table C-3 displays the associations with presence of wheeze and antenatal risk factors. Due to collinearity, each psychosocial risk factor was included separately in a multivariable model, adjusting for key covariates as described. Maternal smoking, number of household smokers, and clinic attended were significantly associated with an increased risk for wheeze; whereas gestational age, and birth weight were found to have a protective association. Full-term births and those with higher birth weight were less at risk of experiencing a wheezing episode.

However, in both the univariate and multivariable models, no psychosocial risk factors were associated with at least one episode of child wheeze.

3.2.1.2 Antenatal psychosocial risk factors and recurrent child wheeze

When recurrent wheeze was considered as the outcome, antenatal psychological distress (OR=1.59, 95% CI: 1.07-2.36) was found significant when considered independently, Table C-4.

However, in the multivariable analysis, none of the key antenatal psychosocial exposures, were associated with recurrent wheeze episodes. The multivariable models adjusted for the same clinical covariates as Table C-4, with the addition of sex and maternal alcohol abuse.

3.2.2 Postnatal psychosocial risk factors and child wheeze

The 6-month postnatal data was used to build the postnatal models, as outcomes at all the scheduled visits were highly correlated (supplementary Table C-10). In addition, a high proportion of wheezing episodes (48.9%) also took place within the first 6 months of life.

The socio-demographics of those who attended and did not attend the 6-month psychosocial visit showed similar characteristics between the two groups, Table C-11 (supplementary tables). There was a higher number of smokers in those that attended the visit relative to those that did not attend. In addition, a higher proportion of those attending the visit were from TC Newman. Psychosocial exposures measured antenatally and at the 12-month postnatal visit were also compared between those attending and not attending the 6-month psychosocial visit. There was no significant difference found in key exposures investigated (Table C-11) when comparing antenatal and postnatal psychosocial risk factors between those included and excluded from postnatal analyses.

3.2.2.1 Postnatal psychosocial risk factors and presence of child wheeze

Psychological distress and IPV were found to be significantly associated with child wheeze, when considered independently.

In the multivariable models, exposure to psychological distress (adjusted OR = 2.10, 95% CI, 1.16 – 3.79) and IPV (adjusted OR =1.60, 95% CI, 1.11 – 2.29) remained significantly associated with child wheeze. Children whose mothers suffered from postnatal psychological distress had a 2-fold increased odds of developing at least one wheeze episode compared to those not exposed, while holding other covariates constant.

3.2.2.2 Postnatal psychosocial risk factors and recurrent child wheeze

From table C-6, the odds of experiencing recurrent wheezing episodes increased by 96% in those whose mothers displayed postnatal depressive symptoms, compared to those whose mothers did not, when considered independently. However, stronger associations were observed when psychological distress (OR=3.12, 95% CI, 1.61 – 6.02) and IPV (OR=2.68, 95% CI, 1.73 – 4.15) was considered.

In the multivariable model, psychological distress and IPV were significantly associated with recurrent wheeze. Postnatal psychological distress had the greatest impact with an adjusted OR of 2.33 (95% CI: 1.09 - 4.95), suggesting that children whose mothers suffer from postnatal psychological distress have a 2.3-fold increased odds in experiencing recurrent wheezing episodes, compared to those not exposed, while holding other covariates constant. Although postnatal IPV exposure also had a substantial influence on recurrent wheeze (adjusted OR= 2.22, 95% CI, 1.35 – 3.63).

4. Discussion

In this peri-urban, low-income area of South Africa, postnatal maternal psychological distress and IPV were strongly associated with early childhood wheezing, even after adjusting for key clinical and socio-demographic exposures. Postnatal maternal depression was associated with recurrent wheeze when considered independently of the clinical covariates. Surprisingly, none of the antenatal psychosocial risk factors were associated with child wheezing. These findings suggest that postnatal maternal psychosocial risk factors increase the risk of early childhood wheeze or recurrent wheeze in a LMIC context.

Several known exposures were also identified as being associated with early wheezing including ETS exposure, low birth weight and prematurity, all of which are well-known risk factors for child wheeze; thus, these associations extend into LMIC settings. The effects of passive smoke, as well as exposure to ETS are widely known[30], and this was confirmed, as maternal smoking resulted in a 2-fold increased odds of recurrent child wheeze. Additional household smokers also placed a child at increased risk for wheezing.

However, antenatal maternal depression and IPV were not associated with either presence of wheeze or recurrent child wheeze. This is inconsistent with previous literature, which found that antenatal psychosocial risk factor exposure predicted child wheeze and asthma diagnosis. Reyes *et al* (2011) found that antenatal psychological distress predicted recurrent wheeze in early stages of life, in both independent and adjusted models. In addition, Ramratnam *et al* (2017), and Mathilda Chiu *et al* (2012), found that antenatal depression was significantly associated with

recurrence of child wheeze. As these studies were conducted in HIC, urban, low-income, and genetically predisposed children, they attributed the associations to biological mechanisms, such as the release of stress hormones, which affect foetal development in utero[4-6].

These biological mechanisms may affect infant lung development and result in obstructed airways through reduced lung capacity[5]. Previous studies have also found that antenatal maternal psychosocial exposure impacts birth weight as well as lung development, which may lead to airway obstruction[13, 31]. As this is the case, there could be an indirect link between antenatal maternal psychosocial health and child wheeze. In this study, no direct link was found between antenatal depression or IPV and child wheeze; however, birth weight and gestational age were found to be confounding variables in the relationship between maternal psychosocial exposure and the onset of child wheeze. Thus, these antenatal psychosocial exposures may be impacting on child wheeze through these biological mechanisms.

When postnatal exposures were considered, maternal psychological distress, as well IPV exposure, were strongly associated with the child experiencing at least one episode wheezing during the 24-month period, as well as recurrent wheeze episodes. These results strengthen the findings of several studies reporting on the relationship between maternal psychosocial risk factors and childhood wheeze and asthma[4, 8-13, 32], and extend the association into a LMIC context.

Potential mechanisms suggested for the association with postnatal maternal psychological distress or IPV exposure and child wheeze have included impaired maternal-child relationship

and a mother's inability to provide care for her child[33]. A mother that is either exposed to IPV or suffering from mental illness is also more likely to engage in harmful behaviours such as drinking or smoking. This was found to be true in the context of this study, as maternal smoking and drinking habits were found to be associated with postnatal psychosocial risk factors.

Antenatal maternal mental health illnesses have also been found to be risk factors for postpartum mental health issues. As antenatal and postnatal maternal mental health were closely correlated in the current study, the effect of postnatal exposure may represent cumulative exposure beginning antenatally and continuing through the postnatal period. An example of this could be biological mechanisms, such as higher cortisol levels in the children due to increased stress hormones being passed from mother to child in-utero[34]. As a result of higher stress levels, the child may not be able to internally cope with stressful events, and thus is more prone to wheezing or asthma diagnosis later in life[35]. This may be further evident if the mother-child interaction is disturbed through maternal psychosocial risk factor exposures; which has been observed in children whose mothers are exposed to postnatal IPV[35]. Due to this study's findings in a LMIC context, biological mechanisms such as cortisol, and stress hormone levels should be investigated in these children to better understand the relationship between maternal psychosocial risk factor exposure and child wheezing.

Notably, there appeared to be a high association with the clinic attended and the onset of child wheeze, which could be linked to differences in psychosocial, environmental, genetic or cultural factors. Those attending the TC Newman clinic, were more likely to display depressive symptoms, psychological distress and be exposed to IPV, compared to those attending

Mbekweni. The TC Newman participants also engaged in higher alcohol consumption and smoking habits compared to those at Mbekweni. The number of wheeze episodes in children was also substantially higher in those attending TC Newman compared to Mbekweni. This indicates that intervention efforts may need to be tailored to community profiles and to specific risk factors present in these communities.

Strengths and limitations

The main limitation was the use of one time-point, the 6-month scheduled visit, to represent the postnatal exposure of psychosocial risk factors. However, as the measurable outcomes of the psychosocial risk factors were correlated over time, it was deemed appropriate to use one time-point. Further research into the subject should consider a longitudinal analysis to investigate the impact of changing postnatal psychosocial risk factors on child wheeze.

In previous studies, maternal or caregiver self-report of wheeze was used to identify episodes, which may have resulted in an under- or over-reporting of wheeze episodes. In the DCHS, respiratory illness symptoms including wheeze were prospectively and actively surveyed by members of the study team, which may improve accuracy of wheeze episode prevalence. The prospective nature of the study provides another strength, especially in terms of antenatal psychosocial measures in relation to child wheeze outcome, as this allows temporality to be considered.

In conclusion, postnatal psychological distress and IPV predicted the development and recurrence of child wheezing in the first 2 years of life. With increasing wheeze prevalence and severity in LMIC settings as well as resource-limited mental health services, it is important to understand the psychosocial risk factors for child wheeze. Understanding how maternal mental health may influence children's respiratory health is an important step in developing effective interventions that lessen the burden of wheeze and asthma in LMIC, such as South Africa.

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6. Tables included in manuscript

Table C- 1 Study participant characteristics

	ALL PARTICIPANTS (N=1143 CHILDREN; 1137 MOTHERS)	PARTICIPANTS FROM MBEKWENI(N=632)	PARTICIPANTS FROM TC NEWMAN (N=511)	P-VALUE
SOCIO-DEMOGRAPHICS				
GIRLS	554 (48.5%)	321 (50.8%)	233 (45.6%)	0.081
RACE: AFRICAN	633 (55.4%)	628 (99.4%)	5 (1.0%)	< 0.0001
RACE: MIXED-ANCESTRY	510 (44.6%)	4 (0.6%)	506 (99.0%)	< 0.0001
HOUSEHOLD INCOME PER MONTH (ZAR)*				
< R1000	430 (37.7%)	264 (41.8%)	166 (32.5%)	< 0.0001
R1000 – R5000	559 (49.0%)	302 (47.8%)	257 (50.3%)	-
> R5000	153 (13.3%)	65 (10.3%)	88 (17.2%)	-
EDUCATION*				
PRIMARY	86 (7.6%)	49 (7.8%)	37 (7.2%)	0.030
SECONDARY	607 (53.2%)	342 (54.2%)	265 (51.9%)	-
COMPLETED SECONDARY	376 (32.9%)	190 (30.1%)	186 (36.4%)	-
ANY TERTIARY	73 (6.4%)	50 (7.9%)	23 (4.5%)	-
SOCIOECONOMIC STATUS QUARTILE*				
LOWEST	271 (23.8%)	184 (29.3%)	87 (17.1%)	< 0.0001
LOW - MODERATE	293 (25.8%)	172 (27.3%)	121 (23.8%)	-
HIGH - MODERATE	290 (25.5%)	146 (23.2%)	144 (28.3%)	-
HIGHEST QUARTILE	283 (24.9%)	127 (20.2%)	156 (30.7%)	-
MATERNAL OR HOUSEHOLD CHARACTERISTICS				
MATERNAL AGE AT DELIVERY	26.07 (22.29 – 31.09)	27.01 (22.66 – 31.96)	24.99 (21.73 – 29.45)	< 0.0001
ANTENATAL MATERNAL SMOKING	306 (26.8%)	39 (6.2%)	267 (52.3%)	< 0.0001
OTHER HOUSEHOLD SMOKERS				
1	396 (34.8%)	230 (36.5%)	166 (32.7%)	< 0.0001
> 2	369 (32.4%)	113 (17.9%)	256 (50.4%)	-
ANTENATAL ALCOHOL USE				
LOW RISK	888 (88.9%)	503 (93.1%)	385 (84%)	< 0.0001
MODERATE RISK	79 (7.9%)	12 (2.2%)	67 (14.6%)	-
HIGH RISK	31 (3.1%)	25 (4.6%)	6 (1.3%)	-
MATERNAL HIV[A]	248 (21.7%)	231 (36.6%)	17 (3.3%)	< 0.0001
FAMILY HISTORY OF ASTHMA	28 (2.5%)	8 (1.3%)	20 (4.0%)	0.004
BIRTH CHARACTERISTICS				
GESTATION (WEEKS)	39 (37 – 40)	39 (37 – 40)	39 (37 – 40)	0.143
PREMATURITY (< 37 WEEKS)	77 (6.8%)	39 (6.3%)	38 (7.5%)	0.422
BIRTHWEIGHT (KG)	3.09 (2.71 – 3.42)	3.16 (2.79 – 3.46)	3.00 (2.63 – 3.36)	0.001
Z-SCORE BIRTHWEIGHT	-0.43 (-1.30 – 0.27)	-0.29 (-1.09 – 0.35)	-0.62 (-1.53 –0.15)	< 0.0001
FEEDING CHOICE				
INITIATED BREASTFEEDING	1 023 (89.9%)	518 (82.2%)	505 (99.4%)	< 0.0001
EXCLUSIVE BREASTFEEDING MONTHS	1.75 (1.00 – 3.50)	1.75 (1.00 – 3.26)	1.75 (1.00 – 3.50)	0.551
MIXED-FEEDING	962 (84.5%)	488 (77.5%)	474 (93.3%)	< 0.0001
CHILD FOLLOW-UP TIME (MONTHS)	23.98 (17.87 – 25.00)	22.24 (16.82 – 24.90)	24.57 (18.04 – 25.00)	< 0.0001
VACCINATIONS				
BCG[B] (BIRTH)	1009/1016 (99.3%)	547/551 (99.3%(	462/465 (99.4%)	0.877
DTAP-IPV-HIB[C] (6-10 WEEKS)	981/986 (99.5%)	542/545 (99.4%)	439/441 (99.5%)	0.831
DTAP-IPV-HIB (10 WEEKS)	967/972 (99.5%)	532/535 (99.4%)	435/437 (99.5%)	0.823
DTAP-IPV-HIB (14 WEEKS)	943/952 (99.2%)	521/525 (99.4%)	422/427 (98.8%)	0.315
DTAP-IPV-HIB (18 MONTHS)	538/654 (82.3%)	324/342 (94.7%)	214/312 (68.6%)	< 0.0001
PCV13[D] (6-10 WEEK)	983/987 (99.6%)	543/546 (99.5%)	440/441 (99.8%)	0.428
PCV13 (14 WEEK)	945/952 (99.3%)	522/525 (99.4%)	423/427 (99.1%)	0.512
PCV13 (9 MONTHS)	867/880 (98.5%)	492/496 (99.2%)	375/384 (97.6%)	0.061

Table C- 1 Continued: Study participant characteristics

	ALL PARTICIPANTS (N=1143 CHILDREN; 1137 MOTHERS)	PARTICIPANTS FROM MBEKWENI(N=634)	PARTICIPANTS FROM TC NEWMAN (N=509)	P-VALUE
WHEEZE EPISODES				
TOTAL WHEEZE EPISODES[1,2,3]	924	420 (45.5%)	504 (54.5%)	-
TOTAL MATERNAL REPORTED EPISODES	437	152 (34.7%)	285 (65.3%)	-
TOTAL LRTI[E] ASSOC. EPISODES	487	268 (55.0%)	219 (45.0%)	-
NO. OF CHILDREN WITH WHEEZE	479 (41.9%)	232 (36.7%)	247 (48.3%)	< 0.0001
NO. OF CHILDREN WITH RECURRENT WHEEZE	186 (21.9%)	78 (16.3%)	108 (29.0%)	< 0.0001

[1]WHEEZE EPISODES OVER TIME: 0-6 MONTHS: N=452; 7-12 MONTHS: N= 229; 13-18 MONTHS: N=151; 19-24 MONTHS: N=92
[2]CRUDE INCIDENCE RATE: 0.497
[3] INCIDENCE RATE OVER 12 MONTH PERIOD: 0-12 MONTHS: 0.6998; 13-24 MONTHS: 0.2839

A. HIV = Human Immunodeficiency Virus; B. BCG = Bacillus Calmette – Guérin vaccine;
C. DTaP - IPV - HiB = Diphtheria, Tetanus, acellular Pertussis, Polio and Haemophilus influenzae type b; D. PCV = Pneumococcal Conjugate Vaccine; E. *LRTI = Lower respiratory Tract Infection*
* Missing data for one participant from Mbekweni
** Missing data for six participants: three from Mbekweni and three from TC Newman

Table C- 2 Antenatal and postnatal psychosocial risk factors

	ALL PARTICIPANTS	PARTICIPANTS FROM MBEKWENI	PARTICIPANTS FROM TC NEWMAN	P-VALUE
ANTENATAL MATERNAL PSYCHOSOCIAL RISK FACTORS (N=1003)				
DEPRESSION	237 (23.6%)	124/540 (23.0%)	113/457 (24.7%)	0.515
PSYCHOLOGICAL DISTRESS	203 (20.2%)	93/545 (17.1%)	110/458 (24.0%)	0.006
IPV[A] (RECENT)[1]	332 (33.5%)	149/537 (27.7%)	183/455 (40.2%)	< 0.0001
PTSD[B] – SUSPECTED PTSD (SUBSET: N=990)[2]	129 (13.0%)	92/536 (17.2%)	37/454 (8.1%)	< 0.0001
PTSD[B] – TRAUMA EXPOSED (SUBSET: N=990)	123 (12.4%)	67/536 (12.5%)	56/454 (12.3%)	-
CHILDHOOD TRAUMA	343 (34.2%)	155/545 (28.4%)	188/458 (41.0%)	< 0.0001
POSTNATAL MATERNAL PSYCHOSOCIAL RISK FACTORS (6-10 WEEKS) (N=692)				
DEPRESSION	119 (17.2%)	62/366 (16.9%)	57/325 (17.5%)	0.835
PSYCHOLOGICAL DISTRESS	69 (10.0%)	18/366 (4.9%)	51/325 (15.7%)	< 0.0001
IPV (RECENT)	177 (26.6%)	78/367 (21.3%)	99/325 (30.5%)	0.006
PTSD – SUSPECTED PTSD (SUBSET: N=198)	9 (4.6%)	8/126 (6.3%)	1/72 (1.4%)	0.326
PTSD – TRAUMA EXPOSED (SUBSET: N=198)	10 (5.1%)	6/126 (4.8%)	4/72 (5.6%)	-
POSTNATAL MATERNAL PSYCHOSOCIAL RISK FACTORS (6 MONTHS) (N=645)				
DEPRESSION	97 (15.0%)	28/326 (8.6%)	69/319 (21.6%)	< 0.0001
PSYCHOLOGICAL DISTRESS	61 (9.5%)	5/324 (1.5%)	56/319 (17.6%)	< 0.0001
IPV (RECENT)	184 (28.6%)	69/324 (21.3%)	115/319 (36.1%)	< 0.0001
PTSD – SUSPECTED PTSD (SUBSET: N=253)	23 (9.1%)	20/150 (13.3%)	3/103 (2.9%)	0.014
PTSD – TRAUMA EXPOSED (SUBSET: N=253)	16 (6.3%)	9/150 (6.0%)	7/103 (6.8%)	-
POSTNATAL MATERNAL PSYCHOSOCIAL RISK FACTORS (12 MONTHS) (N=754)				
DEPRESSION	116 (15.4%)	36/376 (9.6%)	80/341 (23.5%)	< 0.0001
PSYCHOLOGICAL DISTRESS	70 (9.3%)	11/399 (2.8%)	59/355 (16.6%)	< 0.0001
IPV (RECENT)	199 (26.8%)	68/388 (17.5%)	131/354 (37.0%)	< 0.0001
PTSD – SUSPECTED PTSD (SUBSET: N=55)	3 (5.5%)	0/10 (0.0%)	3/45 (6.7%)	0.771
PTSD – TRAUMA EXPOSED (SUBSET: N=55)	4 (7.3%)	0/10 (0.0%)	4/45 (8.9%)	-
POSTNATAL MATERNAL PSYCHOSOCIAL RISK FACTORS (18 MONTHS) (N=663)				
DEPRESSION	65 (10.1%)	22/347 (6.3%)	43/294 (14.6%)	0.001
PSYCHOLOGICAL DISTRESS	53 (8.0%)	7/376 (1.9%)	46/296 (15.5%)	< 0.0001
IPV (RECENT)	144 (21.7%)	62/367 (16.9%)	82/296 (27.7%)	0.001
PTSD – SUSPECTED PTSD (SUBSET: N=235)	18 (7.7%)	16/108 (14.8%)	2/127 (1.6%)	< 0.0001
PTSD – TRAUMA EXPOSED (SUBSET: N=235)	9 (3.8%)	5/108 (4.6%)	4/127 (3.2%)	-
POSTNATAL MATERNAL PSYCHOSOCIAL RISK FACTORS (24 MONTHS) (N=670)				
PSYCHOLOGICAL DISTRESS	51 (7.6%)	10/384 (2.6%)	41/286 (14.3%)	< 0.0001
IPV (RECENT)	144 (21.5%)	69/383 (18.0%)	75/286 (26.2%)	0.011
PTSD – SUSPECTED PTSD (SUBSET: N=281)	16 (5.7%)	10/138 (7.2%)	6/143 (4.2%)	0.153
PTSD – TRAUMA EXPOSED (SUBSET: N=281)	6 (2.1%)	1/138 (0.7%)	5/143 (3.5%)	-

A. IPV = Intimate Partner Violence; B. PTSD = Post-Traumatic Stress Disorder
[1]IPV antenatal lifetime exposure N= 453 (46%); [2]PTSD questionnaire only given to those that have experienced a traumatic event

Table C- 3 Logistic regression: antenatal psychosocial exposures and at least one episode of child wheeze

Predictors of at least one episode of child wheeze, with antenatal psychosocial risk factors as primary exposures		
Variable	**Univariate OR (95% CI)**	**Multivariable OR (95% CI)**
Antenatal Depression	1.13 (0.84, 1.51)	1.11 (0.82, 1.52) [1]
Antenatal Psychological distress	1.29 (0.87, 1.45)	1.22 (0.88, 1.69) [2]
Antenatal Intimate Partner violence	1.07 (0.82, 1.39)	0.99 (0.75, 1.32) [3]
Antenatal Maternal childhood trauma	1.23 (0.95, 1.60)	1.10 (0.83, 1.46) [4]
Antenatal Post-traumatic stress disorder		
No PTSD exposure	REFERENCE	-
Suspect PTSD	1.37 (0.94, 1.99)	1.63 (1.09, 2.44) [5]
Trauma exposed	0.89 (0.61, 1.32)	0.94 (0.62, 1.41) [5]
Maternal age at delivery	0.99 (0.97, 1.01)	-
Maternal HIV status	1.00 (0.75, 1.33)	-
Maternal smoking	1.69 (1.29, 2.19)	1.27 (0.92, 1.75) [6]
Number of household smokers		
None	REFERENCE	-
1 person	1.47 (1.10, 1.96)	1.28 (0.94, 1.73) [6]
2 or more People	1.69 (1.26, 2.27)	1.26 (0.91, 1.76) [6]
Alcohol use	1.30 (0.93, 1.82)	-
Lower risk	REFERENCE	
Moderate risk	1.58 (0.99, 2.51)	-
Higher risk	1.31 (0.64, 2.68)	-
Family history asthma	1.21 (0.57, 2.56)	-
Household income		
<R1000	REFERENCE	-
R1000 – R 5000	0.89 (0.69, 1.14)	-
>R 5000	0.92 (0.63, 1.33)	-
Education		
Primary	REFERENCE	-
Secondary	0.94 (0.60, 1.48)	-
Completed Secondary	0.75 (0.47, 1.21)	-
Tertiary	0.89 (0.47, 1.67)	-
SES quartile		
Lowest	REFERENCE	-
Moderately-low	1.24 (0.89, 1.72)	-
Moderately-high	0.93 (0.66, 1.30)	-
Highest	0.76 (0.54, 1.08)	-
Sex - Female	0.83 (0.65, 1.05)	-
Gestational age	0.95 (0.90, 0.99)	0.95 (0.90, 0.99) [6]
Preterm	1.17 (0.66, 2.06)	-
Birth weight Z-score	0.85 (0.77, 0.95)	0.85 (0.76, 0.95) [6]
Initiated breastfeeding	0.98 (0.66, 1.44)	-
Duration of exclusive breastfeeding	0.96 (0.90, 1.02)	-
DTap-IPV-HIB 6-10 weeks	1.23 (0.20, 7.39)	-
PCV13 6-10 weeks	0.62 (0.14, 2.78)	-
BCG vaccine at birth	1.02 (0.23, 4.57)	-
Clinic attended - TC Newman	1.61 (1.27, 2.04)	1.32 (0.99, 1.76) [6]
Child Follow up time	1.08 (1.06, 1.10)	1.08 (1.06, 1.10) [6]

Multivariable models notation:
[1] N=983. Model 1: Antenatal depression, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[2] N=984. Model 2: Antenatal psychological distress, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[3] N=983. Model 3: Antenatal IPV, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[4] N=989. Model 4: Maternal childhood trauma, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[5] N=154. Model 5: Antenatal PTSD, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[6] N=1122. Model 6: maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.

Table C- 4 Logistic regression: antenatal psychosocial exposures and recurrent child wheeze

Predictors of recurrent child wheeze, with antenatal psychosocial risk factors as primary exposures		
Variable	**Univariate OR (95% CI)**	**Multivariable OR (95% CI)**
Antenatal Depression	1.36 (0.93, 1.98)	1.16 (0.77, 1.77) [7]
Antenatal Psychological distress	1.59 (1.07, 2.36)	1.44 (0.94, 2.22) [8]
Antenatal Intimate Partner violence	1.36 (0.96, 1.92)	1.19 (0.81, 1.75) [9]
Antenatal Maternal childhood trauma	1.35 (0.96, 1.92)	1.05 (0.71, 1.53) [10]
Antenatal Post-traumatic stress disorder		
No PTSD exposure		-
Suspect PTSD	1.26 (0.77, 2.09)	1.87 (1.08, 3.22) [11]
Trauma exposed	0.96 (0.58, 1.61)	1.01 (0.58, 1.78) [11]
Maternal age at delivery	0.99 (0.96, 1.02)	-
Maternal HIV status	0.90 (0.60, 1.34)	-
Maternal smoking	2.50 (1.77, 3.52)	1.82 (1.16, 2.84) [12]
Number of household smokers		
None	REFERENCE	-
1 person	1.58 (1.05, 2.40)	1.06 (0.66, 1.68) [12]
2 or more People	1.89 (1.25, 2.86)	1.01 (0.61, 1.66) [12]
Alcohol use		
Lower risk	REFERENCE	-
Moderate risk	2.49 (1.46, 4.25)	1.88 (1.04, 3.41) [12]
Higher risk	1.33 (0.51, 3.45)	1.34 (0.48, 3.70) [12]
Family history asthma	1.19 (0.43, 3.31)	-
Household income		
<R1000	REFERENCE	-
R1000 – R 5000	0.91 (0.64, 1.31)	-
>R 5000	1.16 (0.71, 1.90)	-
Education		
Primary	REFERENCE	-
Secondary	0.80 (0.45, 1.44)	-
Completed Secondary	0.65 (0.35, 1.20)	-
Tertiary	0.44 (0.17, 1.14)	-
SES quartile		
Lowest	REFERENCE	-
Moderately-low	1.54 (0.98, 2.43)	-
Moderately-high	1.13 (0.71, 1.80)	-
Highest	0.67 (0.40, 1.12)	-
Sex - Female	0.53 (0.38, 0.74)	0.58 (0.40, 0.85) [12]
Gestational age	0.92 (0.87, 0.98)	0.91 (0.84, 0.98) [12]
Preterm	1.59 (0.79, 3.21)	-
Birth weight Z-score	0.86 (0.74, 0.99)	0.88 (0.74, 1.05) [12]
Initiated breastfeeding	1.37 (0.75, 2.49)	-
Duration of exclusive breastfeeding	0.92 (0.84, 1.02)	-
DTap-IPV-HIB 6-10 weeks	-	-
PCV13 6-10 weeks	0.99 (0.10, 9.62)	-
BCG vaccine at birth	0.59 (0.11, 3.27)	-
Clinic attended – TC Newman	2.10 (1.51, 2.92)	1.62 (1.02, 2.57) [12]
Child Follow up time	1.09 (1.06, 1.12)	1.08 (1.05, 1.11) [12]

Multivariable models notation:
[7] N=729. model 7: Antenatal depression, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.
[8] N=729. model 8: Antenatal psychological distress, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.
[9] N=729. model 9: Antenatal IPV, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.
[10] N=733. model 10: Maternal childhood trauma, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.
[11] N=103. model 11: Maternal PTSD, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.
[12] N=734. model 12: maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.

Table C- 5 Logistic regression: postnatal psychosocial exposures and at least one episode of child wheeze

Predictors of at least one episode of child wheeze, with postnatal psychosocial risk factors as primary exposures		
Variable	**Univariate OR (95% CI)**	**Multivariable OR (95% CI)**
Postnatal Depression	1.51 (0.98,2.33)	1.39 (0.88, 2.20) [13]
Postnatal Psychological distress	2.52 (1.44, 4.41)	2.10 (1.16, 3.79) [14]
Postnatal Intimate Partner violence	1.82 (1.29, 2.58)	1.60 (1.11, 2.29) [15]
Postnatal Post-traumatic stress disorder		
No PTSD exposure	REFERENCE	-
Suspect PTSD	1.13 (0.48, 2.67)	1.37 (0.54, 3.45) [16]
Trauma exposed	2.05 (0.72, 5.84)	2.32 (0.77, 7.01) [16]
Maternal age at delivery	0.99 (0.97, 1.01)	-
Maternal HIV status	1.00 (0.75, 1.33)	-
Maternal smoking	1.69 (1.29, 2.19)	1.27 (0.92, 1.75) [17]
Number of household smokers		
None	REFERENCE	-
1 person	1.47 (1.10, 1.96)	1.28 (0.94, 1.73) [17]
2 or more People	1.69 (1.26, 2.27)	1.26 (0.91, 1.76) [17]
Alcohol use	1.30 (0.93, 1.82)	-
Lower risk	REFERENCE	
Moderate risk	1.58 (0.99, 2.51)	-
Higher risk	1.31 (0.64, 2.68)	-
Family history asthma	1.21 (0.57, 2.56)	-
Household income		
<R1000	REFERENCE	-
R1000 – R 5000	0.89 (0.69, 1.14)	-
>R 5000	0.92 (0.63, 1.33)	-
Education		
Primary	REFERENCE	-
Secondary	0.94 (0.60, 1.48)	-
Completed Secondary	0.75 (0.47, 1.21)	-
Tertiary	0.89 (0.47, 1.67)	-
SES quartile		
Lowest	REFERENCE	-
Moderately-low	1.24 (0.89, 1.72)	-
Moderately-high	0.93 (0.66, 1.30)	-
Highest	0.76 (0.54, 1.08)	-
Sex - Female	0.83 (0.65, 1.05)	-
Gestational age	0.95 (0.90, 0.99)	0.95 (0.90, 0.99) [17]
Preterm	1.17 (0.66, 2.06)	-
Birth weight Z-score	0.85 (0.77, 0.95)	0.85 (0.76, 0.95) [17]
Initiated breastfeeding	0.98 (0.66, 1.44)	-
Duration of exclusive breastfeeding	0.96 (0.90, 1.02)	-
DTap-IPV-HIB 6-10 weeks	1.23 (0.20, 7.39)	-
PCV13 6-10 weeks	0.62 (0.14, 2.78)	-
BCG vaccine at birth	1.02 (0.23, 4.57)	-
Clinic attended – TC Newman	1.61 (1.27, 2.04)	1.32 (0.99, 1.76) [17]
Child Follow up time	1.08 (1.06, 1.10)	1.08 (1.06, 1.10) [17]

Multivariable models notation:
[13] N=641. Model 13: Postnatal depression, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[14] N=639. Model 14: Postnatal psychological distress, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[15] N=639. Model 15: Postnatal IPV, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[16] N=250. Model 16: Postnatal PTSD, maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.
[17] N=1122. Model 17: maternal smoking, number of household smokers, gestational age, birthweight, site, follow-up time.

Table C- 6 Logistic regression: postnatal psychosocial exposures and recurrent child wheeze

Predictors of recurrent child wheeze, with postnatal psychosocial risk factors as primary exposures		
Variable	**Univariate OR (95% CI)**	**Multivariable OR (95% CI)**
Postnatal Depression	1.96 (1.15, 3.33)	1.50 (0.82, 2.72) [18]
Postnatal Psychological distress	3.12 (1.61, 6.02)	2.33 (1.09, 4.95) [19]
Postnatal Intimate Partner violence	2.68 (1.73, 4.15)	2.22 (1.35, 3.63) [20]
Postnatal Post-traumatic stress disorder		
No PTSD exposure	REFERENCE	-
Suspect PTSD	1.33 (0.44, 4.02)	1.79 (0.45, 7.15) [21]
Trauma exposed	1.59 (0.38, 6.69)	0.73 (0.08, 6.57) [21]
Maternal age at delivery	0.99 (0.96, 1.02)	-
Maternal HIV status	0.90 (0.60, 1.34)	-
Maternal smoking	2.50 (1.77, 3.52)	1.82 (1.16, 2.84) [22]
Number of household smokers		
None	REFERENCE	-
1 person	1.58 (1.05, 2.40)	1.06 (0.66, 1.68) [22]
2 or more People	1.89 (1.25, 2.86)	1.01 (0.61, 1.66) [22]
Alcohol use		
Lower risk	REFERENCE	-
Moderate risk	2.49 (1.46, 4.25)	1.88 (1.04, 3.41) [22]
Higher risk	1.33 (0.51, 3.45)	1.34 (0.48, 3.70) [22]
Family history asthma	1.19 (0.43, 3.31)	-
Household income		
<R1000	REFERENCE	-
R1000 – R 5000	0.91 (0.64, 1.31)	-
>R 5000	1.16 (0.71, 1.90)	-
Education		
Primary	REFERENCE	-
Secondary	0.80 (0.45, 1.44)	-
Completed Secondary	0.65 (0.35, 1.20)	-
Tertiary	0.44 (0.17, 1.14)	-
SES quartile		
Lowest	REFERENCE	-
Moderately-low	1.54 (0.98, 2.43)	-
Moderately-high	1.13 (0.71, 1.80)	-
Highest	0.67 (0.40, 1.12)	-
Sex - Female	0.53 (0.38, 0.74)	0.58 (0.40, 0.85) [22]
Gestational age	0.92 (0.87, 0.98)	0.91 (0.84, 0.98) [22]
Preterm	1.59 (0.79, 3.21)	-
Birth weight Z-score	0.86 (0.74, 0.99)	0.88 (0.74, 1.05) [22]
Initiated breastfeeding	1.37 (0.75, 2.49)	-
Duration of exclusive breastfeeding	0.92 (0.84, 1.02)	-
DTap-IPV-HIB 6-10 weeks	-	-
PCV13 6-10 weeks	0.99 (0.10, 9.62)	-
BCG vaccine at birth	0.59 (0.11, 3.27)	-
Clinic attended – TC Newman	2.10 (1.51, 2.92)	1.62 (1.02, 2.57) [22]
Child Follow up time	1.09 (1.06, 1.12)	1.08 (1.05, 1.11) [22]

Multivariable models notation:

[18] N=419. Model 18: Postnatal depression, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.

[19] N=419. Model 19: Postnatal psychological distress, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.

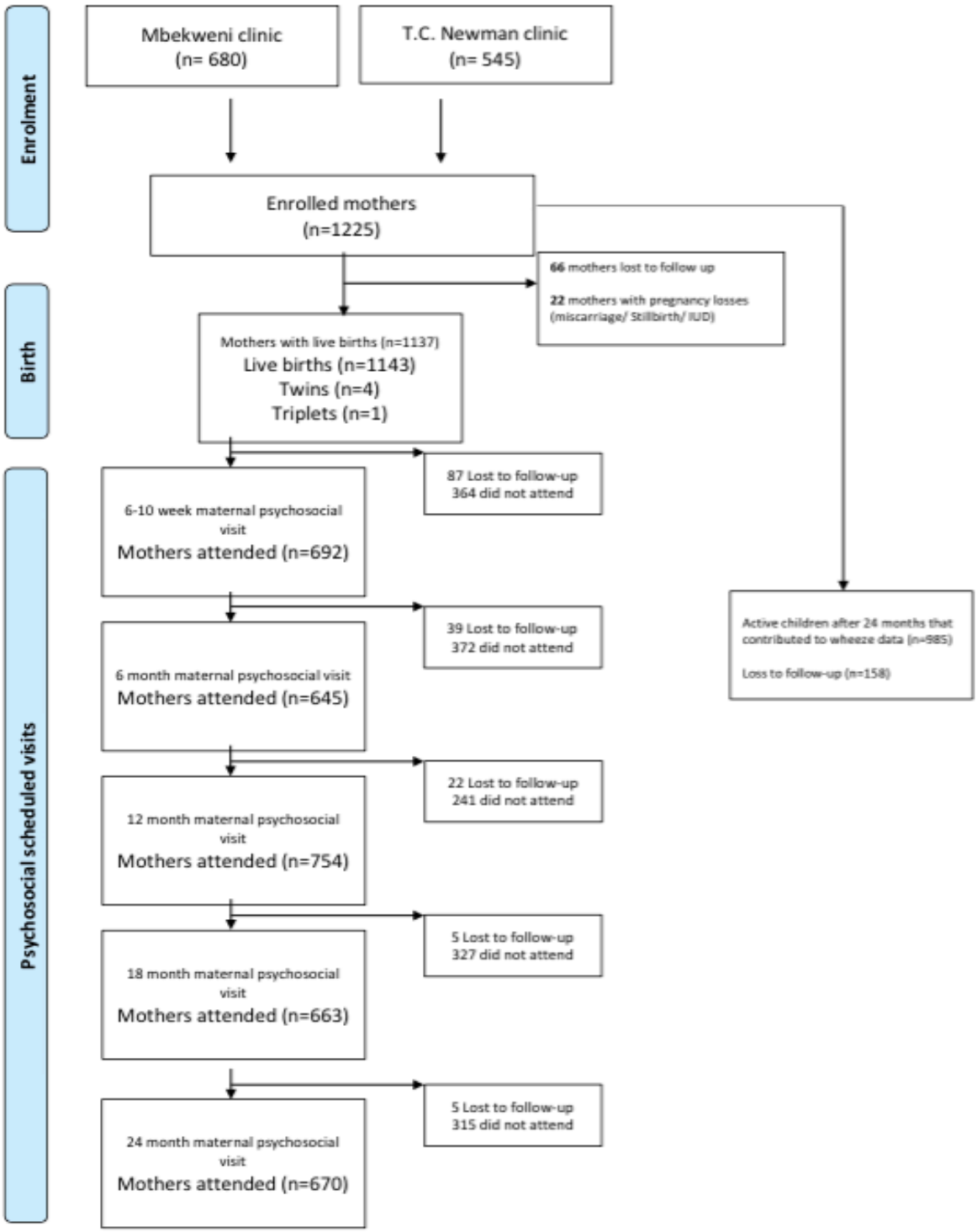
[20] N=419. Model 20: Postnatal IPV, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.

[21] N=156. Model 21: Postnatal PTSD, maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.

[22] N=734. Model 22: maternal smoking, number of household smokers, alcohol use, sex, gestational age, birthweight, site, follow-up time.

7. Supplementary tables/ figures for manuscript

Figure C- 1 Consort diagram of enrolment, lost to follow-up and visit attended



Contingency table were constructed to investigate whether scheduled psychosocial measures were correlated over time. Table C-7 – C-10, considered the maternal depression, psychological distress and IPV measures independently. The contingency table below display odds ratios (OR) and p-value, based on Chi-squared Test of independent tests. With the large odds ratios observed across Table C-7 – C-10, there is sufficient evidence to suggest that the psychosocial risk factor measures are highly associated with other over time. This is further evident from the p-values (<0.05), that suggest that there are significant relationships that exist between the psychosocial risk factor measures over time.

Table C-11, considered whether correlation was present among the psychosocial risk factors. Based on the high odds ratios displayed, there is evidence to suggest that maternal depression, psychological distress and IPV exposure are correlated with one another.

Table C- 7 Chi-squared test of Independence (correlation) between antenatal and postnatal EPDS threshold

EPDS Threshold	**Odds ratios (P-value)**				
	ANC	6-10 weeks	6 month	12 month	18 month
ANC	-	4.66 (<0.0001)	4.75 (<0.0001)	2.67 (<0.0001)	5.19 (<0.0001)
6-10 weeks	4.66 (<0.0001)	-	8.52 (<0.0001)	4.86 (<0.0001)	3.90 (<0.0001)
6 month	4.75 (<0.0001)	8.52 (<0.0001)	-	6.20 (<0.0001)	6.24 (<0.0001)
12 month	2.67 (<0.0001)	4.86 (<0.0001)	6.20 (<0.0001)	-	8.49 (<0.0001)
18 month	5.19 (<0.0001)	3.90 (<0.0001)	6.24 (<0.0001)	8.49 (<0.0001)	-

Table C- 8 Chi-squared test of independence (correlation) between antenatal and postnatal SRQ20 threshold

SRQ20 Threshold	Odds ratios (P-value)					
	ANC	10 weeks	6 month	12 month	18 month	24 month
ANC	-	5.81 (<0.0001)	8.16 (<0.0001)	6.42 (<0.0001)	7.43 (<0.0001)	7.23 (<0.0001)
10 weeks	5.81 (<0.0001)	-	27.61 (<0.0001)	18.66 (<0.0001)	20.93 (<0.0001)	14.45 (<0.0001)
6 month	8.16 (<0.0001)	27.61 (<0.0001)	-	27.08 (<0.0001)	16.06 (<0.0001)	25.07 (<0.0001)
12 month	6.42 (<0.0001)	18.66 (<0.0001)	27.08 (<0.0001)	-	30.21 (<0.0001)	27.84 (<0.0001)
18 month	7.43 (<0.0001)	20.93 (<0.0001)	16.06 (<0.0001)	30.21 (<0.0001)	-	43.03 (<0.0001)
24 month	7.23 (<0.0001)	14.45 (<0.0001)	25.07 (<0.0001)	27.84 (<0.0001)	43.03 (<0.0001)	-

Table C- 9 Chi-squared test of independence (correlation) between antenatal and postnatal IPV threshold

IPV Threshold	Odds ratios (P-value)					
	ANC	10 weeks	6 month	12 month	18 month	24 month
ANC	-	5.76 (<0.0001)	5.89 (<0.0001)	5.06 (<0.0001)	4.01 (<0.0001)	3.29 (<0.0001)
10 weeks	5.76 (<0.0001)	-	10.22 (<0.0001)	4.77 (<0.0001)	4.31 (<0.0001)	4.50 (<0.0001)
6 month	5.89 (<0.0001)	10.22 (<0.0001)	-	11.07 (<0.0001)	6.30 (<0.0001)	5.87 (<0.0001)
12 month	5.06 (<0.0001)	4.77 (<0.0001)	11.07 (<0.0001)	-	6.04 (<0.0001)	5.50 (<0.0001)
18 month	4.01 (<0.0001)	4.31 (<0.0001)	6.30 (<0.0001)	6.04 (<0.0001)	-	6.34 (<0.0001)
24 month	3.29 (<0.0001)	4.50 (<0.0001)	5.87 (<0.0001)	5.50 (<0.0001)	6.34 (<0.0001)	-

Table C- 10 Chi-squared test of independence (correlation) among psychosocial measures

Psychosocial measure	Odds ratios (P-value)					
	EPDS_ANC	EPDS_6m	SRQ20_ANC	SRQ20_6m	IPV_ANC	IPV_6m
EPDS_ANC	-	4.75 (<0.0001)	7.33 (<0.0001)	5.81 (<0.0001)	2.69 (<0.0001)	1.99 (<0.0001)
EPDS_6m	4.75 (<0.0001)	-	2.97 (<0.0001)	23.31 (<0.0001)	2.83 (<0.0001)	2.55 (<0.0001)
SRQ20_ANC	7.33 (<0.0001)	2.97 (<0.0001)	-	8.16 (<0.0001)	2.73 (<0.0001)	2.51 (<0.0001)
SRQ20_6m	5.81 (<0.0001)	23.31 (<0.0001)	8.16 (<0.0001)	-	4.62 (<0.0001)	5.86 (<0.0001)
IPV_ANC	2.69 (<0.0001)	2.83 (<0.0001)	2.73 (<0.0001)	4.62 (<0.0001)	-	5.89 (<0.0001)
IPV_6m	1.99 (<0.0001)	2.55 (<0.0001)	2.51 (<0.0001)	5.86 (<0.0001)	5.89 (<0.0001)	-

In order to justify the use of 6-month psychosocial data to represent postnatal exposure, demographic information, as well as the psychosocial risk factor exposures antentally and 12 months postpartum, were compared between those who attended and those who did not attend the 6-month psychosocial visit.

Based on Table C-11, there were similar household income and education levels between the two groups. In addition, alcohol consumption was similar between those attending and not attending the 6-month psychosocial visit. The birth characteristics were also similar, as the median birthweight and gestation age was 3.09kg and 39 weeks respectively. However, maternal smoking did differ between the two groups, as 33% of those who attended the 6-month psychosocial visit smoked, while only 19% of those that did not attend smoked.

When considering the antenatal psychosocial risk factors, maternal depression and psychological distress were similar between the two groups. However, antenatal IPV was statistically different between the two groups. Although, all the psychosocial risk factors, measured at the 12-month visit, were similar between the two groups.

As the majority of characteristics were similar between the two groups, utilising the 6-month psychosocial data as a proxy for postnatal exposure was appropriate.

Table C- 11: Socio-demographic comparison between those attending and not attending 6-month psychosocial visit

VARIABLE	ATTENDED 6-MONTH PSYCHOSOCIAL VISIT (N=646)	DID NOT ATTEND 6-MONTH PSYCHOSOCIAL VISIT (N=497)	P-VALUE
CLINIC – TC NEWMAN	319 (49.8%)	192 (38.6%)	<0.0001
FEMALE	313 (48.5%)	241 (48.5%)	0.990
HOUSEHOLD INCOME PER MONTH (ZAR)			
< R1000	260 (40.2%)	170 (34.0%)	0.091
R1000 – R5000	307 (47.5%)	252 (50.7%)	-
> R5000	79 (12.2%)	74 (14.9%)	-
EDUCATION			
PRIMARY	46 (7.1%)	40 (8.0%)	0.075
SECONDARY	365 (56.5%)	239 (48.1%)	-
COMPLETED SECONDARY	197 (30.5%)	177 (35.6%)	-
ANY TERTIARY	38 (5.9%)	35 (7.5%)	-
SOCIO-ECONOMIC STATUS QUARTILE			
LOWEST	157 (24.3%)	114 (22.9%)	0.024
LOW - MODERATE	175 (27.1%)	118 (23.7%)	-
HIGH - MODERATE	175 (27.1%)	115 (23.1%)	-
HIGHEST QUARTILE	139 (21.5%)	144 (29.0%)	-
MATERNAL OR HOUSEHOLD CHARACTERISTICS			
MATERNAL AGE AT DELIVERY	26.35 (22.21 – 31.01)	25.92 (22.33 – 31.11)	0.4875
MATERNAL SMOKING	211 (32.7%)	95 (19.1%)	<0.0001
OTHER HOUSEHOLD SMOKERS			
ONE SMOKER	242 (37.5%)	154 (31.0%)	<0.0001
TWO OR MORE SMOKERS	243 (37.6%)	126 (25.4%)	-
ANTENATAL ALCOHOL USE			
LOWER RISK	375 (88%)	513 (89%)	0.750
MODERATE RISK	32 (7.6%)	47 (8.2%)	-
HIGHER RISK	15 (3.6%)	16 (2.8%)	-
MATERNAL HIV	138 (21.4%)	110 (22.1%)	0.754
FAMILY HISTORY OF ASTHMA (ATOPY)	14 (2.2%)	14 (2.9%)	0.467
BIRTH CHARACTERISTICS			
GESTATION (WEEKS)	39 (37 – 40)	39 (37 – 40)	0.572
PREMATURITY (< 37 WEEKS)	39 (5.9%)	38 (8.0%)	0.161
BIRTHWEIGHT (KG)	3.09 (2.70 – 3.42)	3.09 (2.73 – 3.41)	0.772
FEEDING CHOICE			
INITIATED BREASTFEEDING	591 (91.5%)	432 (87.8%)	0.041
EXCLUSIVE BREASTFEEDING MONTHS	2 (0.75 – 4)	1.5 (1 – 3)	0.241
MIXED-FEEDING	591 (91.5%)	371 (75.4%)	<0.0001
PSYCHOSOCIAL MEASURES AT ANTENATAL AND 12 MONTH VIST			
ANTENATAL DEPRESSION	147 (25.3%)	90 (21.6%)	0.169
POSTNATAL DEPRESSION (12 MONTH VISIT)	79 (16.4%)	37 (15.8%)	0.853
ANTENATAL PSYCHOLOGICAL DISTRESS	120 (20.7%)	81 (19.6%)	0.677
POSTNATAL PSYCHOLOGICAL DISTRESS (12 MONTH VISIT)	43 (8.7%)	27 (10.5%)	0.420
ANTENATAL IPV	294 (50.8%)	159 (38.5%)	<0.0001
POSTNATAL IPV (12 MONTH VISIT)	130 (26.6%)	69 (27.2%)	0.878

Part D: Appendices

Appendix 1: Human Research Ethics Committee (HREC) approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arlefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

06 June 2017

HREC REF: 387/2017

Dr M Lesosky
Department of Public Health & Family Medicine
Level 3, FHS

Dear Dr Lesosky

PROJECT TITLE: INVESTIGATING ASSOCIATIONS OF MATERNAL MENTAL HEALTH ON WHEEZE THROUGH 2 YEARS OF AGE IN A SOUTH AFRICAN BIRTH COHORT STUDY (Master's candidate-R MacGinty)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 June 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, R MacGinty will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

Signed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 387/2017

Appendix 2: Edinburgh Post-Natal Depression (EPDS) questionnaire (English version)

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

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

Mother Participant ID: _ _ _ _ / _ / _ /_ _

Child Participant ID: _ _ _ _ / _ / _ /_ _

Date: _ _ / _ _ _ / _ _ _ _ DD / MMM / YYYY

	Address	
	Phone Number	

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Example:

Here is an example, already completed.
I have felt happy:

☐ Yes, all the time
☐ Yes, most of the time
☐ No, not very often
☐ No, not at all

This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.

IN THE PAST 7 DAYS:		
1	I have been able to laugh and see the funny side of things	☐ As much as I always could ☐ Not quite so much now ☐ Definitely not so much now ☐ Not at all
2	I have looked forward with enjoyment to things	☐ As much as I ever did ☐ Rather less than I used to ☐ Definitely less than I used to ☐ Hardly at all
3*	I have blamed myself unnecessarily when things went wrong	☐ Yes, most of the time ☐ Yes, some of the time ☐ Not very often ☐ No, never
4	I have been anxious or worried for no good reason	☐ No, not at all ☐ Hardly ever

		☐ Yes, sometimes ☐ Yes, very often
5*	I have felt scared or panicky for no very good reason	☐ Yes, quite a lot ☐ Yes, sometimes ☐ No, not much ☐ No, not at all
6*	Things have been getting on top of me	☐ Yes, most of the time I haven't been able to cope at all ☐ Yes, sometimes I haven't been coping as well as usual ☐ No, most of the time I have coped quite well ☐ No, I have been coping as well as ever
7*	I have been so unhappy that I have had difficulty sleeping	☐ Yes, most of the time ☐ Yes, sometimes ☐ Not very often ☐ No, never
8*	I have felt sad or miserable	☐ Yes, most of the time ☐ Yes, quite often ☐ Not very often ☐ No, not at all
9*	I have been so unhappy that I have been crying	☐ Yes, most of the time ☐ Yes, quite often ☐ Only occasionally ☐ No, never
10*	The thought of harming myself has occurred to me	☐ Yes, quite often ☐ Sometimes ☐ Hardly ever ☐ Never

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

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

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

Appendix 3: Self-Reporting Questionnaire (SRQ20) (English version)

CRF0X: SRQ-20

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

1	Do you often have headaches?	☐ YES ☐ NO
2	Is your appetite poor?	☐ YES ☐ NO
3	Do you sleep badly?	☐ YES ☐ NO
4	Are you easily frightened?	☐ YES ☐ NO
5	Do your hands shake?	☐ YES ☐ NO
6	Do you feel nervous, tense or worried?	☐ YES ☐ NO
7	Is your digestion poor?	☐ YES ☐ NO
8	Do you have trouble thinking clearly?	☐ YES ☐ NO
9	Do you feel unhappy?	☐ YES ☐ NO
10	Do you cry more than usual?	☐ YES ☐ NO
11	Do you find it difficult to enjoy your daily activities?	☐ YES ☐ NO
12	Do you find it difficult to make decisions?	☐ YES ☐ NO
13	Is your daily work suffering?	☐ YES ☐ NO
14	Are you unable to play a useful part in life?	☐ YES ☐ NO

15	Have you lost interest in things?	☐ YES ☐ NO
16	Do you feel that you are a worthless person?	☐ YES ☐ NO
17	Has the thought of ending your life been on your mind?	☐ YES ☐ NO
18	Do you feel tired all the time?	☐ YES ☐ NO
19	Do you have uncomfortable feelings in your stomach?	☐ YES ☐ NO
20	Are you easily tired?	☐ YES ☐ NO

Appendix 4: Intimate Partner Violence (IPV) Questionnaire (English version)

CRF0X: Intimate Partner Violence

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

Mother Participant ID: _ _ _ _ / _ / _ /_ _

Child Participant ID: _ _ _ _ / _ / _ /_ _

Date: _ _ / _ _ _ / _ _ _ _ DD / MMM / YYYY

Introduction

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

	EMOTIONAL ABUSE	
	SCORING for Questions 1-4: 1 = Never; 2 = Once; 3 = Few; 4 = Many *Tick the most appropriate answer.*	
1	Has your husband or boyfriend ever insulted you or made you feel bad about yourself? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
2	Has your husband or boyfriend ever belittled or humiliated you in front of other people? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
3	Has your husband or boyfriend ever done things to scare or intimidate you on purpose for example by the way he looked at you, by yelling and smashing things? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
4	Has your husband or boyfriend ever threatened to hurt you? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
	SCORING for Question 5: 1 = Yes; 2 = No	
5	Have any of these things happened in the past 12 months?	1 Yes 2 No

PHYSICAL ABUSE **SCORING for Questions 6-10:** **1 = Never** **2 = Once** **3 = Few** **4 = Many**		
6	Has your husband or boyfriend ever slapped you or thrown something at you which could hurt you? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
7	Has your husband or boyfriend ever pushed or shoved you? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
8	Has your husband or boyfriend ever hit you with a fist or with something else which could hurt you? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
9	Has your husband or boyfriend ever kicked, dragged, beaten, choked or burnt you? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
10	Has your husband or boyfriend ever threatened to use or actually used a gun, knife or other weapon against you? Did this happen many times, a few times, once or did it not happen?	1 Never 2 Once 3 Few 4 Many
SCORING for Question 11: 1 = Yes; 2 = No		
11	Have any of these things happened <u>in the past 12 months?</u>	1 Yes 2 No

SEXUAL ABUSE		
SCORING for Questions 12-14: 1 = Never; 2 = Once; 3 = Few; 4 = Many		
12	Has your husband or boyfriend ever physically forced you to have sex when you did not want to? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
13	Have you ever had sex with your husband or boyfriend when you did not want to because you were afraid of what he might do? Did this happen many times, a few times, once, or did it not happen?	1 Never 2 Once 3 Few 4 Many
14	Has your husband or boyfriend ever forced you to do something sexual that you found degrading or humiliating?	1 Never 2 Once 3 Few 4 Many
SCORING for Question 15: 1 = Yes; 2 = No		
15	Have any of these things happened <u>in the past 12 months?</u>	1 Yes 2 No

COMPLETION OF QUESTIONNAIRE		
16	This questionnaire has asked you about many difficult things. How has answering these questions made you feel?	☐ GOOD/BETTER ☐ BAD/WORSE ☐ SAME/NO DIFFERENCE
17	Do you have any comments, or is there anything else you would like to add?	
	_____ _____ _____ _____ _____	

We know these were difficult questions to answer, but it is only by hearing from women themselves that we can really understand about their health and experiences of intimate partner violence. Thank you for helping us, and for taking the time to complete this questionnaire.

A study staff member will be providing you with a list of organisations that provide support, legal advice and counselling services to women in your area. You can take the information home with you, or leave it at the clinic if you prefer. Please do contact these services if you would like to talk with anyone about your situation. The services are free, and they will keep anything that you say to them private.

Appendix 5: Maternal Childhood Trauma Questionnaire – Short Form (CTQ – SF) (English version)

Visit: ANC 2	Mother Participant ID: _ _ _ _ / _ /_ /_ _	Date: _ _ / _ _ _ / _ _ _ _	
	Child Participant ID: _ _ _ _ / _ /_ /_ _	DD / MMM / YYYY	

Childhood Trauma Questionnaire – Short Form (CTQ-SF)

These questions ask about some of your experiences growing up **as a child and a teenager**. For each question, circle the number that best describes how you feel. Although some of these questions are of a personal nature, please try to answer as honestly as you can. Your answers will be kept confidential.

	When I was growing up, …	**Never True**	**Rarely**	**Sometimes True**	**Often True**	**Very Often True**
1	I didn't have enough to eat.	**1**	**2**	**3**	**4**	**5**
2	I knew there was someone to take care of me and protect me	**1**	**2**	**3**	**4**	**5**
3	People in my family called me things like "stupid", "lazy", or "ugly".	**1**	**2**	**3**	**4**	**5**
4	My parents were too drunk or high to take care of me.	**1**	**2**	**3**	**4**	**5**
5	There was someone in my family who helped me feel important or special.	**1**	**2**	**3**	**4**	**5**
6	I had to wear dirty clothes.	**1**	**2**	**3**	**4**	**5**
7	I felt loved.	**1**	**2**	**3**	**4**	**5**
8	I thought that my parents wished I had never been born.	**1**	**2**	**3**	**4**	**5**
9	I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	**1**	**2**	**3**	**4**	**5**
10	There was nothing I wanted to change about my family.	**1**	**2**	**3**	**4**	**5**
11	People in my family hit me so hard that it left bruises or marks.	**1**	**2**	**3**	**4**	**5**
12	I was punished with a belt, a board, a cord, or some hard object.	**1**	**2**	**3**	**4**	**5**
13	People in my family looked out for each other.	**1**	**2**	**3**	**4**	**5**
14	People in my family said hurtful or insulting things to me.	**1**	**2**	**3**	**4**	**5**
15	I believe that I was physically abused.	**1**	**2**	**3**	**4**	**5**
16	I had the perfect childhood.	**1**	**2**	**3**	**4**	**5**
17	I got hit or beaten so badly that it was noticed by someone like a	**1**	**2**	**3**	**4**	**5**

	teacher, neighbour, or doctor.					
18	I felt that someone in my family hated me.	**1**	**2**	**3**	**4**	**5**
19	People in my family felt close to each other.	**1**	**2**	**3**	**4**	**5**
20	Someone tried to touch me in a sexual way, or tried to make me touch them.	**1**	**2**	**3**	**4**	**5**
21	Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	**1**	**2**	**3**	**4**	**5**
22	I had the best family in the world.	**1**	**2**	**3**	**4**	**5**
23	Someone tried to make me do sexual things or make me watch sexual things.	**1**	**2**	**3**	**4**	**5**
24	Someone molested me.	**1**	**2**	**3**	**4**	**5**
25	I believe that I was emotionally abused.	**1**	**2**	**3**	**4**	**5**
26	There was someone to take me to the doctor if I needed it.	**1**	**2**	**3**	**4**	**5**
27	I believe that I was sexually abused	**1**	**2**	**3**	**4**	**5**
28	My family was a source of strength and support.	**1**	**2**	**3**	**4**	**5**

Appendix 6: Modified PTSD Symptom Scale (MPSS) Questionnaire (English version)

CRF0X: Modified PTSD Symptom Scale (MPSS)

Visit: ANC 2	Mother Participant ID: _ _ _ _ / _ / _ /_ _	Date: _ _ / _ _ _/ _ _ _ _	
	Child Participant ID: _ _ _ _ / _ / _ /_ _	DD / MMM / YYYY	

Modified PTSD Symptom Scale (MPSS)

To be completed AFTER completion of the Life Events Questionnaire

INSTRUCTIONS:

After completing the **Life Events Questionnaire**, please select **one event** from that questionnaire that up to the present has been the **most** troublesome, disturbing or distressing.

What type of event was this?

_____

_____

If there was no such event in the Life Events Questionnaire, have you been exposed to any **other** event in your lifetime that involved actual or threated death or serious injury, or threat to the physical integrity of yourself or others?

☐ No
☐ Yes – *if "Yes", what type of event was this?*

_____

_____

How did you experience this event? (Please tick one)

☐ There was no such event *(Do not continue with this questionnaire)*
☐ I experienced the event myself
☐ I witnessed the event
☐ I heard of a significant other having experienced the event

(If there has been no such event in your lifetime, you are not required to complete this questionnaire)

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

FREQUENCY

0 = Not at all **1** = Once per week or less/a little bit/once in a while **2** = Two to four times per week/somewhat/half the time **3** = Five or more times per week/very much/almost always		
1	Have you had recurrent or intrusive distressing thoughts or recollections about the event(s)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
2	Have you been having recurrent bad dreams or nightmares about the event(s)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
3	Have you had the experience of suddenly reliving the event(s), flashbacks of it, acting or feeling as if it were re-occurring?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
4	Have you been intensely EMOTIONALLY upset when reminded of the event(s) (includes anniversary reactions)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
5	Have you persistently been making efforts to avoid thoughts or feelings associated with the event(s)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
6	Have you persistently been making efforts to avoid activities, situations, or places that remind you of the	[0] Not at all [1] Once per week or less/a little bit/once in a while

	event(s)?	[2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
7	Are there any important aspects of the event(s) that you still cannot recall?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
8	Have you markedly lost interest in free time activities since the event(s)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
9	Have you felt detached or cut off from others around you since the event(s)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
10	Have you felt that your ability to experience emotions is less (e.g., unable to have loving feelings, do you feel numb, can't cry when sad, etc.)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
11	Have you felt that any future plans or hopes have changed because of the event(s)? (e.g., no career, marriage, children, or long life?)	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always

12	Have you been having persistent difficulty falling or staying asleep?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
13	Have you been continuously irritable or having outbursts of anger?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
14	Have you been having persistent difficulty concentrating?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
15	Are you overly alert (e.g., check to see who is around you, etc.) since the event(s)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
16	Have you been jumpier, or more easily startled since the event(s)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
17	Have you been having intense	

	PHYSICAL reactions (e.g. sweaty, heart palpitations) when reminded of the event(s)?	[0] Not at all [1] Once per week or less/a little bit/once in a while [2] Two to four times per week/somewhat/half the time [3] Five or more times per week/very much/almost always
18	How long have these symptoms bothered you?	☐ Less than 1 month ☐ 1-3 months ☐ 3 months - 1 year ☐ Longer than 1 year

Appendix 7: Journal submission guidelines:

Pediatric Pulmonology

Edited By: Thomas Murphy

Impact Factor: 2.758

ISI Journal Citation Reports © Ranking: 2016: 19/121 (Pediatrics); 26/59 (Respiratory System)

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Preliminary brief communications will be considered if the articles contain information which would be considered a major breakthrough in the field.

We do not publish research funded by tobacco companies.

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Editors generally commission Reviews and State of the Art papers, but uninvited submissions are also welcome, particularly if the submission outlines an important and topical subject with a focus on recent advances. Reviews should be limited to 4,000 words, while State of the Art papers should be limited to 5,000 words (not including the abstract or references). We ask that the abstracts for these manuscript types do not exceed 250 words. There is no set limit on images, tables, or references for these types of manuscripts.

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NOTICE TO AUTHORS OF CASE REPORTS: Pediatric Pulmonology is temporarily closing submissions of Case Reports. We will not consider new case report manuscripts during the period of July 15, 2017 to October 15, 2017. Case Report submission will re-open on October 15, 2017.

Pediatric Pulmonology will review case report manuscripts that present unique, paradigm-changing, or novel accounts of infantile or childhood disorders. Priority for selection for publication will be given to the following categories:.

1. Novel therapies and outcomes for cystic fibrosis
2. Novel disorders or outcomes of ChILD, NEHI, ABCA3 disorders, and surfactant disorders
3. Novel congenital malformations
4. Novel genetic disorders
5. Novel therapies or outcomes for other disorders

There is not a related format for a case series. Manuscripts of this nature will be treated as original articles or reviews and will compete with other manuscripts in these categories.

Case reports should be concise (a maximum of 1,000 words, not including the abstract or references), and contain a maximum of two images and/or tables. The summary/abstract should not exceed 100 words. Case Reports should contain no more than five (5) references. Authorship of case reports shall be limited to three (3). Physicians who participated in the care, but did not contribute to the writing of the manuscript may be listed under acknowledgements. Informed consent must be documented. Authors should note that most accepted Case Reports will be published online only, and not in a print edition.

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Editors and members of the Editorial Board may make editorial comments on individual articles or on a group of articles published in the same issue. Editorials (including pro/con debates) from authors who are not part of the editorial team are also welcome as submissions to the Journal. These narrowly focused articles should discuss an article that was recently published, or that is soon to be published. The commentary should discuss specific issues within a subject area rather than the whole field, while explaining the implications of the article and putting it in context. Opinions must be factually based. These types of manuscripts should be limited to 1,500 words (not including the abstract or references). There is no limitation on the number of tables, images or references for these types of manuscripts.

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We encourage letters that offer criticism of published material in an objective, constructive, and educational manner conducive to further exchanges. Such letters will only be considered if they are in reference to an article published within the previous six months. Letters may also discuss matters of general interest pertaining to the field of pediatric pulmonology, or may consist of brief reports of truly unique cases. Note that we do not publish original, previously unpublished data as letters. If appropriate, a copy will be sent to the author(s) referred to in the letter, so that they may respond. Letters to the Editor should not exceed 1,000 words (not including the abstract or references), and may contain a small table or single image. Letters should contain no more than five (5) references.

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Acknowledgements: Technical assistance, advice, referral of patients, etc. may be briefly acknowledged at the end of the text under "Acknowledgements."

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Sample references:
Standard journal article
Landau IL, Morgan W, McCoy KS, Taussig LM. Gender related differences in airway tone in children. Pediatr Pulmonol 1993;16:31-35.
Book with authors
Voet D, Voet JG. 1990. Biochemistry. New York: John Wiley & Sons. 1223 p.
Book with editors
Coutinho A, Kazatch Kine MD, editors. Autoimmunity physiology and disease. New York. Wiley-Liss; 1994. 459 p.
Chapter from a book
Hausdorf G. Late effects of anthracycline therapy in childhood: evaluation and current therapy. In: Bricker JT, Green DM, D'Angio GJ, editors. Cardiac toxicology after treatment for childhood cancer. New York: Wiley-Liss; 1993. p 73-86.
For a book reference only include the page numbers that have direct bearing on the work described.

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- a concise introductory statement outlining the specific aims of the study and providing a discussion of how each aim was fulfilled;
- a succinct description of the working hypothesis;
- a detailed explanation of assumptions and choices made regarding study design and methodology;
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- a concise comparison of the results with those of conflicting or confirmatory studies in the literature;
- a brief summary of the limitations of the scientific methods and results; and
- a brief discussion of the implications of the findings for the field and for future studies.
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Tables should not be included in the Main Document, but submitted as a separate DOC or RTF file. Number tables with Arabic numbers consecutively and in order of appearance. Type each table double-spaced on a separate page, captions typed above the tabular material. Symbols for units should be used only in column headings. Do not use internal horizontal or vertical lines; place horizontal lines between table caption and column heading, under column headings, and at the bottom of the table (above the footnotes if any). Use footnote letters (a, b, c, etc.) in consistent order in each table. All tables should be referred to in the text. Do not submit tables as photographs and do not separate legends from tables.

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