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Association of Maternal Depression and Anxiety with Toddler Social-Emotional and Cognitive Development in South Africa: A prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058135
Article Type:	Original research
Date Submitted by the Author:	07-Oct-2021
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Keywords:	Community child health < PAEDIATRICS, Depression & mood disorders < PSYCHIATRY, Anxiety disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY

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Title: Association of Maternal Depression and Anxiety with Toddler Social-Emotional and Cognitive Development in South Africa: A prospective cohort study

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Financial Support: This research was supported by the Bill and Melinda Gates Foundation (WPF) and grants U01HD055154, U01HD045935, U01HD055155, and U01HD045991 issued by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and grant U01AA016501 issued by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Dr. Lauren Shuffrey is supported by K99HD103910 issued by the Eunice Kennedy Shriver National Institute Of Child Health & Human Development. Dr. Ayesha Sania is supported by UH3OD023279-05S1, re-entry supplement from Office of the Director, NIH, and Office of Research on Women Health (ORWH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests: The authors have no competing interests to declare.

Data availability: Data are available on request.

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Abstract:

Objective: A robust literature has identified associations between prenatal maternal depression and adverse child social-emotional and cognitive outcomes. The majority of prior research is from high-income countries despite increased reporting of perinatal depression in low and middle income countries (LMICs). Additionally, despite the comorbidity between depression and anxiety, few prior studies have examined their joint impact on child neurodevelopment. The objective of the current analysis was to examine associations between prenatal maternal depression and anxiety with child social-emotional and cognitive development in a cohort from the Western Cape Province of South Africa.

Design: Prenatal maternal depression and anxiety were measured using the Edinburgh Postnatal Depression Scale (EPDS) and the State-Trait Anxiety Scale (STAI) at 20 – 24 weeks' gestation. Child neurobehavior was assessed at age 3 using the Brief Infant Toddler Social Emotional Assessment (BITSEA) and the Bayley Scales of Infant Development (BSID-III). We used linear regression models to examine the independent and joint association between prenatal maternal depression, anxiety, and child developmental outcomes.

Results: Participants consisted of 600 maternal-infant dyads (274 females; gestational age at birth: 38.89 weeks \pm 2.03). Children born to mothers with both prenatal depression and trait anxiety had the largest increase in social-emotional problems (mean difference: 4.66; 95% CI 3.43, 5.90) compared to children born to mothers with no prenatal depression or trait anxiety, each condition alone, or compared to mothers with depression and state anxiety. Additionally, children born to mothers with prenatal maternal depression and trait anxiety had the greatest reduction in mean cognitive scores on the BSID-III (mean difference: -1.04; 95% CI -1.99, -0.08).

Conclusions: The observed association between comorbid prenatal maternal depression and chronic anxiety with subsequent child social-emotional and cognitive development underscores the need for targeting mental health support in perinatal women in LMICs to improve long-term child neurobehavioral outcomes.

Strengths and limitations of this study

- Strengths include prospective evaluation of maternal depression and anxiety symptoms during pregnancy and prospective assessment of cognitive and social-emotional outcomes within the same cohort in a large sample of mother-children pairs.
- Limitations include a lack of data on maternal mental health assessments postnatally and mother-child dyadic measures, which are potential mediators of the relationship between prenatal maternal depression, prenatal maternal anxiety, and child developmental outcomes.

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3 **Key Questions:**
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5 What is already known about this subject?
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- 7 • Prenatal maternal depression and anxiety are associated with adverse child social-emotional and cognitive outcomes.
- 8 • The majority of prior research in this domain is from high-income countries.
- 9 • In South Africa an estimated 35% women report prenatal depression.
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12 What does this study add?
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- 14 • Our results from a South African cohort study suggest comorbid prenatal maternal depression and chronic anxiety have a greater impact on child social-emotional and cognitive development than either condition alone or than comorbid prenatal maternal depression and transitory anxiety during pregnancy.
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19 How might this impact on clinical practice?
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- 21 • These results underscore the need for targeting mental health in perinatal women in low and middle income countries to improve long-term child neurobehavioral outcomes.
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52 **Keywords:** prenatal depression, prenatal anxiety; social-emotional development; cognitive
53 development
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Introduction

Decades of research on the early origins of behavior has promoted the concept that the prenatal environment has a profound impact on one's risk for the development of neurodevelopmental or psychiatric disorders^{1 2}. Several prior studies have identified associations between prenatal maternal depression and increased risk for social-emotional problems and decrements in cognitive development. However, the majority of prior research in this domain is from high-income countries (HICs), despite increased reporting of perinatal depression in low and middle income countries (LMICs) including South Africa where an estimated 35% women report prenatal depression^{3 4}. Additionally, despite the comorbidity between depression and anxiety, few prior studies have examined their joint impact on child neurodevelopment.

Several studies in HICs have identified associations between prenatal maternal depression, anxiety, and offspring behavioral, social-emotional, and cognitive development⁵. Specifically, a meta-analysis demonstrated adverse effects of prenatal maternal depression and anxiety on child social-emotional problems, with odds ratios of 1.79 and 1.50 respectively⁶. Prenatal maternal depression and anxiety are also associated with cognitive and language deficits^{7 8}, delayed motor development⁸, emotional and behavior dysregulation⁹⁻¹¹, inattention and hyperactivity¹²⁻¹⁴, and difficult temperament¹⁵. A more recent meta-analysis not only confirmed prior reports, but also found that the effects of perinatal maternal depression extend beyond infancy through adolescence¹⁶.

The developmental origins of health and disease (DOHaD) model posits that maternal psychological distress during pregnancy (e.g. perceived stress, depression, anxiety, trauma) may result in changes in hypothalamic pituitary adrenal (HPA) axis function and upregulation of inflammatory processes with downstream effects on offspring perinatal brain development and

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3 behavior¹⁷. These risk factors may be exacerbated in LMICs such as South Africa, where both
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5 poverty and perinatal mental health disorders are highly prevalent^{18 19}. Specifically, in South
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7 Africa maternal mood disorders have been linked to structural and community stressors
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9 associated with markers of poverty including less than a high school education, lack of social
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11 support, alcohol use, family stress, food insecurity, lack of partner involvement, and intimate
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13 partner violence²⁰⁻²⁴. There are few prior studies that have examined the impact of prenatal
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15 maternal mental health on offspring social-emotional or cognitive development in South Africa.
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17 While the few prior studies reported significant harmful effects of prenatal maternal stress or
18
19 perinatal maternal depression, there is still a significant gap in the literature in research
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21 examining the impact of prenatal maternal psychological health on child neurobehavioral
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23 development in resource-poor communities^{20 25 26}. Additionally, to our knowledge no prior South
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25 African studies have examined the joint effect of prenatal maternal depression and anxiety on
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27 child neurobehavioral outcomes. Research examining the long-term impact of prenatal maternal
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29 depression and anxiety on child behavioral and cognitive outcomes is critical for providing
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31 justification to local public health services for targeting mental health support in perinatal
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33 women from underserved communities.
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40 The objective of the current analysis was to determine if prenatal maternal depression and
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42 state or trait anxiety were associated with child social-emotional problems or cognitive
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44 development at approximately three years of age in a South African cohort from the Western
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46 Cape.
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Materials and Methods

Participants. Participants were a subset of infants with available outcome data at age 3 enrolled in the Safe Passage Study conducted by the Prenatal Alcohol and SIDS and Stillbirth (PASS) Network, a multi-center study investigating the role of prenatal exposure in risk for sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol spectrum disorders. Eligibility criteria for the Safe Passage study included the ability to provide informed consent in English or Afrikaans, 16 years of age or older at the time of consent, and a gestational age between 6 weeks and 40 weeks at the time of consent based on estimated delivery date²⁷. Informed consent was obtained for the Safe Passage study and from a parent or legal guardian of each participant for developmental follow-up assessments. Ethical approval was obtained for both time points from the Health Research Ethics Committee of Stellenbosch University and the New York State Psychiatric Institute.

Maternal Assessments.

Maternal-infant chart abstraction, demographic, and socioeconomic measures. Maternal-infant medical charts were abstracted to obtain maternal age at delivery, gestational age at birth, mode of delivery, and the infant's biological sex. Measures to collect prenatal alcohol, tobacco, and recreational drug exposure have been previously described^{27 28}. Through study specific case report forms, participants indicated demographic and socioeconomic information including race, maternal educational attainment, household crowding (persons per room in household), access to running water inside the house, prenatal care during pregnancy, and marital status.

Self-reported depression and anxiety measures. Information regarding maternal mental health during pregnancy was obtained at 20 – 24 weeks' gestation. Depressive symptoms were

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2
3 measured using the Edinburgh Postnatal Depression Scale (EPDS), a depression screening tool
4 developed to specifically assess depressive symptoms in perinatal women where higher scores
5 indicate more severe depressive symptoms^{29 30}. The EPDS is widely used and has been validated
6 in English and Afrikaans in South Africa^{29 31}. Prior studies have used a cut-off score of ≥ 12 or \geq
7 13 to be indicative of major depression within perinatal women living in South Africa^{29 31}.
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14 Maternal anxiety symptoms were measured using the State-Trait Anxiety Inventory (STAI)³², an
15 anxiety screening tool to distinguish anxiety symptoms from depressive symptoms which has
16 also been validated in both languages³³. The STAI has two subscales, state anxiety which reflects
17 the participant's current state of anxiety when completing the questionnaires and trait anxiety,
18 which is thought to be consistent across time and reflect personality traits. In HICs, the STAI has
19 a cut-off score of ≥ 40 on both the state anxiety and trait anxiety subscales to indicate a threshold
20 for clinical levels of anxiety. Based on these prior studies, we used a cutoff of ≥ 13 to indicate
21 maternal depression, a cutoff of > 40 on the STAI-state subscale to indicate state anxiety, and a
22 cutoff of > 40 on the STAI-trait subscale to indicate trait anxiety.
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38 Toddler Developmental Assessments.

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40 *Bayley Scales of Infant Development III Screening Test.* The Bayley Scales of Infant
41 Development III (BSID-III screening test) were designed as a rapid assessment of cognitive,
42 language, and motor functioning in infants and young children in order to determine if a child's
43 development is within normal limits and identify risk for developmental delay. The BSID-III
44 screening test has high test-retest reliability: Cognitive (0.85), Receptive Language (0.88),
45 Expressive Language (0.88), Fine Motor (0.82), and Gross Motor (0.86)³⁴. Although the BSID-
46 III screening test does not identify degree of impairment, the cut-off points indicate whether a
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3 child shows competence in age-appropriate tasks, evidence of emerging age-appropriate skills,
4 and evidence of being at risk for developmental delay. The BSID has been validated and widely
5 used throughout South Africa^{35 36}.
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10 *Brief Infant Toddler Social Emotional Assessment (BITSEA)*. The Brief Infant-Toddler
11 Social and Emotional Assessment (BITSEA) is a 42-item parental report measure of social-
12 emotional development, behavioral problems, and delays in competence³⁷. Domains assessed
13 within the BITSEA include: externalizing (activity/impulsivity, aggression/defiance, peer
14 aggression), internalizing (depression/withdrawal, anxiety, separation distress, inhibition to
15 novelty), dysregulation (sleep, negative emotionality, eating, sensory sensitivity), and
16 competence (compliance, attention, imitation/play, mastery motivation, empathy, and pro-social
17 peer relations)³⁷. Findings from the BITSEA validation study provide preliminary support for the
18 BITSEA as a reliable and valid brief screener for infant-toddler social-emotional and behavioral
19 problems in addition to delays in competence³⁸. When used in socioeconomically and ethnically
20 diverse community-based populations, the BITSEA demonstrated excellent test-retest reliability
21 and good inter-rater agreement between parents³⁷.
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40 Statistical Analyses. Using multiple linear regression models, we estimated independent and
41 joint effects of maternal depression and state and trait anxiety on social-emotional problem,
42 social emotional competence, and cognitive development scores. Two, separate four-level
43 categorical prenatal maternal mental health variables were created to assess the impact of
44 prenatal maternal depression, trait anxiety, and state anxiety. We created a prenatal maternal
45 depression and trait anxiety variable with four categories: (1) *No Prenatal Depression or Trait*
46 *Anxiety* (n=199; 33.17%, Reference Category), (2) *Prenatal Depression Only* (106; 17.67%), (3)
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3 *Prenatal Trait Anxiety Only* (n=68; 11.33%) and (4) *Prenatal Maternal Depression and Trait*
4 *Anxiety* (n=227; 37.83%) (Table 1). In separate models we additionally examined the
5
6 independent and joint effects of prenatal maternal depression and state anxiety. We created a
7
8 prenatal maternal depression and state anxiety variable with four categories: (1) *No Prenatal*
9
10 *Depression or State Anxiety* (n=248; 41.33%; Reference Category), (2) *Prenatal Depression*
11
12 *Only* (n=237; 39.50%), (3) *Prenatal State Anxiety Only* (n=19; 3.17%) and (4) *Prenatal*
13
14 *Maternal Depression and State Anxiety* (n=96; 16%) (Table 1). For each regression model, either
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16 *No Prenatal Maternal Depression or Trait Anxiety* or *No Prenatal Maternal Depression and*
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18 *State Anxiety* was set as the reference category. Minimally adjusted models included sex,
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20 gestational age at birth, and age at follow up as covariates. Fully adjusted models additionally
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22 controlled for prenatal maternal alcohol use, prenatal maternal tobacco use, maternal
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24 employment status at delivery, maternal educational attainment at delivery, parity, and the
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26 household crowding index. We used missing indicator methods and median imputation to
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28 account for missing categorical and continuous covariate data, respectively (described in Table 1).
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30 All analyses were performed in SAS software version 9.4 (SAS Institute, Cary NC).
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Results

Maternal and Child Demographic Characteristics. The participants included in the present analysis consisted of mothers and their infant born between April 2014 and August 2015 from the Western Cape Province of South Africa who participated in a follow-up study to examine social-emotional development and cognitive development at approximately three years of age. A total of n=18 mother-infant dyads were excluded due to missing maternal prenatal mental health data. The final sample consisted of 600 maternal-infant dyads (274 females; gestational age at birth: 38.89 weeks \pm 2.03) (Table 1).

Child Social-Emotional Development. Based on the BITSEA problem scale percentile rank score of 26 or higher, 50% of children (310/614) were classified as having a “possible problem”. Based on the BITSEA competence scale percentile rank score of 15 or lower, 5% (34/614) of children were classified in the “possible deficit/delay range” (Table 2). There were no significant sex differences in social-emotional problems on the BITSEA, however girls had significantly higher social-emotional competence compared to boys (mean difference: 0.38, CI: 0.05, 0.71, $p = 0.03$)

Association between Prenatal Maternal Depression, Trait Anxiety, and Child Social-Emotional Development. Compared to children born to mothers with no prenatal depression or trait anxiety, children born to mothers with prenatal depression and trait anxiety had the greatest increase in social-emotional problems (mean difference: 4.66; 95% CI 3.43, 5.90), followed by prenatal maternal trait anxiety only (mean difference: 3.87; 95% CI 2.07, 5.66), and finally prenatal maternal depression only (mean difference: 2.76; 95% CI 1.23, 4.29) in minimally adjusted models. These associations remained significant in fully adjusted models where similarly the greatest increase in social-emotional problems was in the comorbid prenatal

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3 maternal depression and trait anxiety group (mean difference: 4.33; 95% CI 2.90, 5.67), followed
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5 by prenatal maternal trait anxiety only (mean difference: 3.23; 95% CI 1.19, 5.27), with the
6
7 smallest mean difference for prenatal maternal depression only group (mean difference: 2.64;
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9 95% CI 1.02, 4.27) as compared to the no prenatal depression or trait anxiety group (Figure 1).
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11 Additional significant predictors in the multivariate models were parity of 3 or greater which was
12
13 associated with a reduction in social-emotional problems (mean difference: -3.02, 95% CI -4.63,
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15 -1.40) and low continuous smoking during pregnancy which was associated with an increase in
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17 social-emotional problems (mean difference: 1.39, 95% CI 0.039, 2.74). There were no
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19 significant associations between prenatal maternal depression, trait anxiety, and child social-
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21 emotional competence.
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26 *Association between Prenatal Maternal Depression, State Anxiety, and Child Social-*
27 *Emotional Development.* Compared to children born to mothers with no prenatal depression or
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29 state anxiety, children born to mothers with comorbid prenatal depression and state anxiety had
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31 the greatest increase in social-emotional problems (mean difference: 4.29; 95% CI 2.73, 5.84).
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33 Children born to mothers with prenatal depression only also had increased social-emotional
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35 problems compared to mothers with no prenatal depression or state anxiety (mean difference:
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37 2.71; 95% CI 1.51, 3.88). These associations remained significant in fully adjusted models
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39 (prenatal depression and state anxiety: 3.90 mean increase (95% CI 2.19, 5.60); prenatal
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41 depression only: 2.58 mean increase (95% CI 1.34, 3.82)) (Figure 1). Additional significant
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43 predictors in the multivariate models were parity of 3 or greater which was associated with a
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45 mean reduction in social-emotional problems (mean difference: -3.22, 95% CI -4.86, -1.58), low
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47 continuous smoking during pregnancy which was associated with a mean increase in social-
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49 emotional problems (mean difference: 1.44; 95% CI 0.075, 2.81), and finally less than a high
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3 school education (some primary school only) which was associated with a mean increase in
4 social-emotional problems (mean difference: 3.47; 95% CI 0.248, 6.70). However, there was no
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6 significant mean difference in social-emotional problems on the BITSEA in children born to
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8 mothers with prenatal state anxiety only. There were also no significant associations between
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10 prenatal maternal depression, state anxiety, and social-emotional competence.
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15 *Child Cognitive, Language, and Motor Development.* Based on normative cognitive
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17 cutoff scores defined by the BSID-III, 4% of children (24/615) were classified as at-risk, 73% of
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19 children were classified as emerging (448/615), and 23% of children were classified as
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21 competent (143/615) (Table 2). Risk classification percentages were similar across all
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23 subdomains, expressive language: 5% , receptive language: 4%, gross motor: 3%, and fine
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25 motor: 3%. There were no significant sex differences in child cognitive scores.
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29 *Association between Prenatal Maternal Depression, Trait Anxiety, and Child Cognitive,*
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31 *Language, and Motor Development.* Compared to children born to mothers with no prenatal
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33 depression or trait anxiety, children born to mothers with comorbid prenatal depression and trait
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35 anxiety had decreased mean cognitive scores on the BSID-III (mean difference: -1.04; 95% CI -
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37 1.99, -0.08). Results remained significant in the fully adjusted model (mean difference; -1.11;
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39 95% CI -2.13, -0.09) (Figure 2). Low continuous prenatal maternal alcohol use was also
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41 associated with a mean reduction in cognitive scores (mean difference: -1.30; 95% CI -2.36, -
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43 0.24).
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47 *Association between Prenatal Maternal Depression, State Anxiety, and Child Cognitive,*
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49 *Language, and Motor Development.* Compared to children born to mothers with neither prenatal
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51 depression nor trait anxiety, there was no significant reduction in cognitive scores for children
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3 born to mothers with prenatal depression only, prenatal trait anxiety only, or combined prenatal
4 depression and trait anxiety in either the minimally or fully adjusted models.
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7 **Discussion**

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10 In summary, we found the greatest increase in child social-emotional problems in
11 children born to women with comorbid prenatal depression and trait anxiety compared to women
12 with no prenatal depression or trait anxiety, prenatal depression alone, or prenatal trait anxiety
13 alone. We additionally found a significant effect of comorbid prenatal maternal depression and
14 state anxiety on increased child social-emotional problems; however, we found no effect of
15 prenatal maternal state anxiety in the absence of prenatal maternal depression on child social-
16 emotional problems. Finally, we reported children born to mothers with prenatal maternal
17 depression and trait anxiety had lower cognitive scores on the BSID-III, but we did not find an
18 association between prenatal maternal depression alone on cognitive outcomes at 3-years of age.
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31 Our finding linking prenatal maternal depression and anxiety to social-emotional risk
32 parallels two recent South African studies linking increased prenatal maternal stressors to
33 increased behavioral problems in children with an odds ratio of 2.52, but not before 4 years of
34 age²⁵ and increased perinatal depression to aggressive behaviors at 60 months of age²⁰. Our
35 findings are also largely consistent with a recent meta-analysis of studies predominately
36 conducted in HICs, which found prenatal maternal depression and anxiety were associated with
37 increased social-emotional problems in offspring with larger effect sizes for prenatal maternal
38 depression (OR 1.79; 95% CI 1.61 - 1.99) compared to prenatal maternal anxiety (OR 1.50, 95%
39 CI, 1.36 - 1.64)⁶. We found the greatest increase in child social-emotional problems in children
40 born to women with comorbid prenatal depression and trait anxiety and no effect of prenatal
41 maternal state anxiety in the absence of prenatal maternal depression on child social-emotional
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3 problems. Our results are suggestive that chronic anxiety measured via trait anxiety may be more
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5 predictive of child neurobehavioral outcomes than a single measurement of concurrent anxiety
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7 during pregnancy.
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10 A prior meta-analysis⁶ also found stronger effects of prenatal maternal depression and
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12 anxiety on child outcomes when sociodemographic risk factors such as low-income, lower levels
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14 of parental education, or single family households, were highest⁶. Similarly, we found that lower
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16 levels of maternal education, low continuous tobacco use during pregnancy, and low continuous
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18 alcohol use during pregnancy were associated with increased social-emotional problems in
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20 children at three years of age. Intriguingly, maternal parity of 3 or greater was protective and
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22 associated with a mean reduction in social-emotional problems which may be due to reduced
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24 depression and anxiety levels in women with higher parity, changes in the perception of their
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26 child's behavior due to having multiple children, or additional social opportunities during sibling
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28 interactions^{39 40}.
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33 The Drakenstein Child Health Study based in the Western Cape found approximately
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35 50% of the overall sample (369/731) were categorized as having cognitive delay at two years of
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37 age based on cutoffs defined by United States normative data²⁶. Better cognitive outcomes were
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39 associated with higher maternal education, older child age, a primigravid mother, and higher
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41 socioeconomic status whereas prenatal maternal depression was associated with a 1.03 SD (95%
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43 CI -1.94 to -0.12) reduction in cognitive scores on the Bayley Scales of Infant and Toddler
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45 Development at two years of age²⁶. Similar to the Drakenstein Child Health Study²⁶, we found
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47 children born to mothers with prenatal maternal depression and trait anxiety had lower cognitive
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49 scores on the BSID-III compared to the no prenatal maternal depression or trait anxiety group.
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52 However, in contrast we did not find an association between prenatal maternal depression alone
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3 on cognitive outcomes at 3-years of age. More recently, a large home-visiting intervention study
4 based in Cape Town examined the effect of prenatal maternal depression only, postnatal
5 maternal depression only (birth – 60 months), or recurrent pre- and postnatal maternal
6 depression only (birth – 60 months), or recurrent pre- and postnatal maternal
7 depression. This study also accounted for several other risk factors including intimate partner
8 violence, HIV status, and alcohol use on child social behaviors, language skills, and cognitive
9 development. No associations were found between maternal depression at any time point with
10 children's language or cognitive development at 36 or 60 months of age²⁰. However, children of
11 never depressed mothers had lower aggressive behaviors on the Child Behavior Checklist at 60
12 months of age than children of mothers with postnatal depression only or perinatal depression²⁰.
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24 There are several biological mechanisms which can explain prior studies and our current
25 findings linking prenatal maternal depression and anxiety with child social-emotional behaviors
26 and cognitive development including increased prenatal maternal inflammation and/or increased
27 cortisol production⁴¹⁻⁵⁰. Pregnancy is associated with increased inflammatory processes and
28 increased placental cortisol production with reduced maternal hypothalamic–pituitary–adrenal
29 (HPA) axis sensitivity to stress^{41 42}. However, prenatal maternal depression may upregulate
30 inflammatory processes and/or cortisol production. Maternal cortisol can cross the placenta
31 resulting in increased inflammation^{41 42} and/or affect the developmental of limbic regions, which
32 are associated with social and emotional processes⁵¹. In animal models, increased
33 proinflammatory proteins have been associated with widespread changes in perinatal brain
34 development such as with volume reductions in gray and white matter, decreased density of
35 GABAergic neurons, reduced synaptic pruning, and network dysfunction with potential
36 downstream effects on neurobehavioral development⁴³⁻⁵⁰.
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3 While we report an association of prenatal maternal depression and anxiety with child
4 social-emotional and cognitive development from a prospective cohort study with a fairly large
5 sample of participants, there are several limitations within the current study that are worth
6 noting. Although, prior studies have emphasized the importance of measuring childhood trauma,
7 maternal stress, and social support within communities with several heterogeneous risk factors³,
8 these measures were not collected as part of the original NIH Safe Passage Study or our recent
9 follow-up study. Therefore, we could not examine their effects or consider maternal social
10 support as a potential moderator of resilient neurodevelopmental outcomes. There is also robust
11 literature examining both postpartum depression (PPD) and the early mother-infant relation in
12 shaping child outcomes. Two prior studies in South Africa demonstrated maternal intrusiveness
13 and coerciveness mediated the association between maternal PPD and early childhood
14 attachment^{52 53}. In the current study, we did not collect data postnatally between birth and three
15 years of age. Additionally, we did not collect postnatal information on maternal depression,
16 anxiety, or stress. Therefore, we cannot draw conclusions regarding the combined effect of the
17 pre- and postnatal environment on child neurodevelopmental outcomes. Strengths of the current
18 analyses include our large sample size, evaluation of both cognitive and social-emotional
19 outcomes within the same cohort, finally the detailed prospective collection of both depression
20 and anxiety symptoms during pregnancy²⁷ in addition to other potential confounders.
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45 Our results suggest comorbid prenatal maternal depression and chronic anxiety have a
46 greater impact on child social-emotional and cognitive development than either condition alone
47 or than comorbid prenatal maternal depression and transitory anxiety during pregnancy. These
48 findings are supported by a robust literature within the DOHaD framework linking perturbations
49 in the gestational environment to later neurodevelopmental or psychiatric sequelae. Our results
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3 also lend support for future intervention studies aimed at perinatal mental health interventions
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5 targeting maternal depressive and anxiety symptoms to improve long-term child social-emotional
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7 and cognitive developmental outcomes.
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Table 1 - Sociodemographic characteristics		
	Mean ± SD or N (%)	N and Percent Missing (%)
Maternal Characteristics		
Maternal Age (years)	25.26 ± 5.91	0 (0%)
Maternal Body Mass Index (BMI)		0 (0%)
	BMI <18.5 (kg/m ²)	62 (10.33%)
	BMI 18.5-25 (kg/m ²)	282 (47%)
	BMI 25-30 (kg/m ²)	132 (22%)
	BMI >30 (kg/m ²)	124 (20.67%)
Parity		0 (0%)
	Parity <1	218 (36.33%)
	Parity =1	196 (32.67%)
	Parity =2	103 (17.17%)
	Parity ≥3	83 (13.83%)
Antenatal care visits		0 (0%)
	antenatal care visit <3	49 (8.17%)
	antenatal care visit 3-6	389 (64.83%)
	antenatal care visit >6	162 (27%)
Cesarean Section	106 (17.70%)	1 (0.1%)
Education		0 (0%)
	Some primary school	43 (7.167%)
	Some high school	405 (67.57%)
	Completed high school	119 (19.83%)
	Beyond high school	33 (5.5%)
Married	290 (48.33%)	0 (0%)
Employed	172 (28.67%)	0 (0%)
Adjusted Household Crowding	1.56 ± 0.72	2 (0.33%)
Depression (Edinburgh ≥13)	333 (55%)	0 (0%)
Anxiety (State-Trait Anxiety Inventory ≥40)	115 (19.17%)	0 (0%)
Maternal Prenatal Alcohol Use		0 (0%)
	Non drinking	245 (46.93%)
	Moderate-high continuous drinking	122 (23.37%)
	Low continuous drinking	26 (4.98%)
	Quit early drinking	129 (24.71%)
Maternal Prenatal Tobacco Use		2 (0.33%)
	Non smoking	227 (37.97%)

	Moderate-high continuous smoking	132 (22.07%)	
	Low continuous smoking	222 (37.12%)	
	Quit early smoking	17 (2.84%)	
	Raw Maternal Edinburgh Score	12.99 ± 5.73	0 (0%)
	Raw Maternal State Anxiety Score	31.23 ± 10.24	0 (0%)
	Raw Maternal Trait Anxiety Score	40.63 ± 10.63	0 (0%)
	Depression - Trait Anxiety Groups		0 (0%)
	No depression or trait anxiety	199 (33.17%)	
	Depression alone	106 (17.67%)	
	Trait anxiety alone	68 (11.33%)	
	Depression and trait anxiety	227 (37.83%)	
	Depression - State Anxiety Groups		0 (0%)
	No depression or state anxiety	248 (41.33%)	
	Depression alone	237 (39.50%)	
	State anxiety alone	19 (3.17%)	
	Depression and state anxiety	96 (16%)	
Infant Characteristics			
	Infant Sex		0 (0%)
	Male	326 (54.33%)	
	Female	274 (45.67%)	
	Gestational age at birth (weeks)	38.89 ± 2.03	0 (0%)
	Infant Birth weight (grams)	2980.65 ± 564.65	2 (0.33%)
	Follow-up age (months)	38.29 ± 2.96	0 (0%)
	Adjusted follow-up age (months)	38.14 ± 0.016	0 (0%)
Table 2. Neurodevelopmental Outcome Raw Scores and At-risk Groups			
	Raw Mullen Scores		
	Gross motor	25.47 ± 4.34	
	Fine motor	23.55 ± 4.08	
	Problem solving	13.40 ± 6.77	
	Receptive language	21.69 ± 5.10	
	Expressive language	21.27 ± 3.78	
	At-Risk Categories		
	Gross motor	21 (3.5%)	
	Fine motor	18 (3%)	
	Cognitive	24 (4.0%)	
	Receptive language	33 (5.50%)	
	Expressive language	25 (4.17%)	

Brief Infant Toddler Social-Emotional Assessment (BITSEA)		
	Social Emotional Problem	13.4 ± 6.77
	Competence	19.55 ± 2.07
At-Risk Categories		
	Social Emotional Problem	310 (50%)
	Competence	34 (5%)

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3 **Contributors:** WPF and HJO acquired funding for and designed the work. LCS, AS, NHB, ML,
4 YR, PES, HJO, and WPF conceptualized the work. MP, PES, CDP, and HJO acquired the data.
5
6 LCS, NHB, and WPF led in data collection oversight and quality control. AS, LCS, and YR
7
8 analyzed the data. All authors contributed to the interpretation of data and drafting the work and
9
10 revising it critically for important intellectual content. All authors approved the final manuscript
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12 and agree to be accountable for all aspects of the work.
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19 **Acknowledgements:** We would like to acknowledge Lucy Brink, J. David Nugent, and Daianna
20
21 Rodriguez for their database and administrative support. We would also like to thank all of the
22
23 families who participated in this research study for making this work possible.
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28 **Ethics statements**

29 **Patient consent for publication**

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31 Not applicable.
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38 **Ethics approval**

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40 Ethics approval was received from the Institutional Review Boards and ethics review committees
41
42 at Stellenbosch University (N16-08-101 and N06-10-210) and the New York State Psychiatric
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44 Institute (5338). All participants provided informed written consent at both time points (prenatal
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46 and postnatal) before inclusion in the study.
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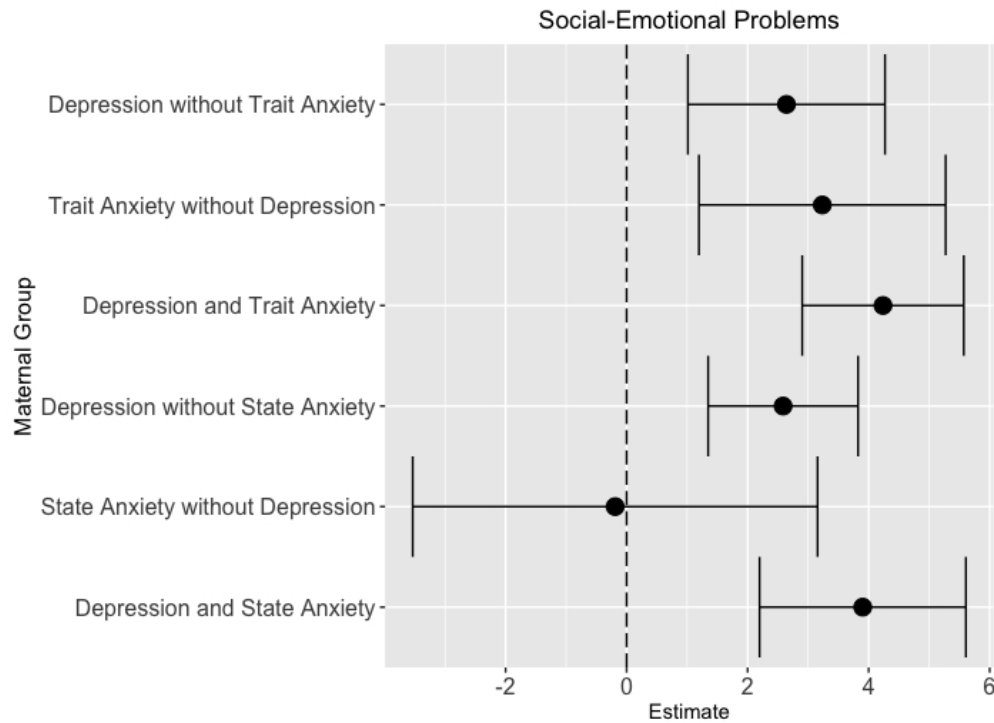
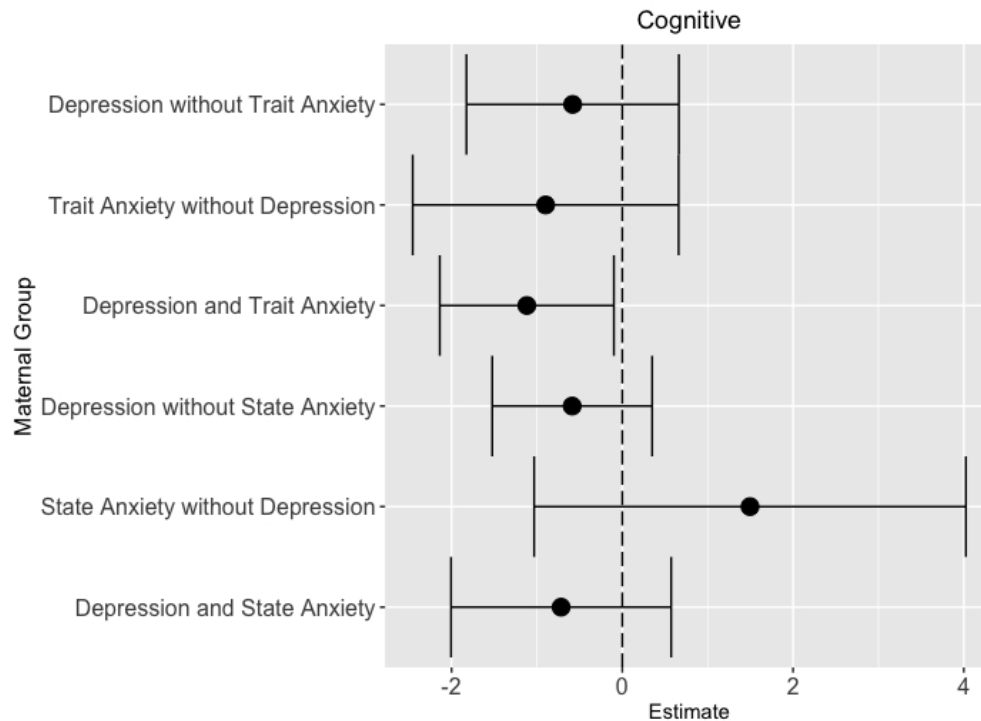


Figure 1. Association between prenatal maternal depression, prenatal maternal anxiety, and child social-emotional problems measured by the BITSEA. Each line plot depicts the mean difference and their confidence interval for child social-emotional problems (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

247x181mm (72 x 72 DPI)



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Figure 2. . Association between prenatal maternal depression, prenatal maternal anxiety, and child cognitive development measured by the BSID-III Screening Test. Each line plot depicts the mean difference and their confidence interval for child cognitive development (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	2 3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7 - 9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 - 9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7 - 9 N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9 - 10
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 - 10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9 - 10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	9 - 10 9 - 10 10 10 N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11 11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9, 11 - 13 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11 - 13
2			(b) Report category boundaries when continuous variables were categorized	N/A
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11 - 13
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	14
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
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18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	17
20				
21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1
23				
24				

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26 *Give information separately for exposed and unexposed groups.

27
28 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
29 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
30 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
31 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
32 available at <http://www.strobe-statement.org>.
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BMJ Open

Association of Maternal Depression and Anxiety with Toddler Social-Emotional and Cognitive Development in South Africa: A prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058135.R1
Article Type:	Original research
Date Submitted by the Author:	22-Feb-2022
Complete List of Authors:	Shuffrey, Lauren; Columbia University Irving Medical Center, Psychiatry; New York State Psychiatric Institute, Division of Developmental Neuroscience Sania, Ayesha; Columbia University Irving Medical Center, Psychiatry; New York State Psychiatric Institute, Division of Developmental Neuroscience Brito, Natalie; New York University, Department of Applied Psychology Potter, Mandy; Stellenbosch University Faculty of Medicine and Health Sciences, Obstetrics and Gynaecology Springer, Priscilla; Stellenbosch University, Paediatrics and Child Health Lucchini, Maristella ; Columbia University Irving Medical Center, Psychiatry; New York State Psychiatric Institute, Neuroscience Rayport, Yael; Columbia University Irving Medical Center, Department of Psychiatry; New York State Psychiatric Institute, Neuroscience Du Plessis, Carlie; Stellenbosch University Faculty of Medicine and Health Sciences, Department of Obstetrics and Gynaecology Odendaal, H. J.; Stellenbosch University Faculty of Medicine and Health Sciences, Obstetrics & Gynaecology Fifer, William; Columbia University Irving Medical Center, Psychiatry; New York State Psychiatric Institute, Neuroscience
Primary Subject Heading:	Global health
Secondary Subject Heading:	Mental health, Paediatrics
Keywords:	Community child health < PAEDIATRICS, Depression & mood disorders < PSYCHIATRY, Anxiety disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY

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Title: Association of Maternal Depression and Anxiety with Toddler Social-Emotional and Cognitive Development in South Africa: A prospective cohort study

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Financial Support: This research was supported by the Bill and Melinda Gates Foundation (WPF) and grants U01HD055154, U01HD045935, U01HD055155, and U01HD045991 issued by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and grant U01AA016501 issued by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Dr. Lauren Shuffrey is supported by K99HD103910 issued by the Eunice Kennedy Shriver National Institute Of Child Health & Human Development. Dr. Ayesha Sania is supported by UH3OD023279-05S1, re-entry supplement from Office of the Director, NIH, and Office of Research on Women Health (ORWH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests: The authors have no competing interests to declare.

Data availability: Data are available upon reasonable request.

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Abstract:

Objective: A robust literature has identified associations between prenatal maternal depression and adverse child social-emotional and cognitive outcomes. The majority of prior research is from high-income countries despite increased reporting of perinatal depression in low and middle income countries (LMICs). Additionally, despite the comorbidity between depression and anxiety, few prior studies have examined their joint impact on child neurodevelopment. The objective of the current analysis was to examine associations between prenatal maternal depression and anxiety with child social-emotional and cognitive development in a cohort from the Western Cape Province of South Africa.

Design: Prenatal maternal depression and anxiety were measured using the Edinburgh Postnatal Depression Scale (EPDS) and the State-Trait Anxiety Scale (STAI) at 20 – 24 weeks' gestation. Child neurobehavior was assessed at age 3 using the Brief Infant Toddler Social Emotional Assessment (BITSEA) and the Bayley Scales of Infant Development Screening Test (BSID-III ST). We used linear regression models to examine the independent and joint association between prenatal maternal depression, anxiety, and child developmental outcomes.

Results: Participants consisted of 600 maternal-infant dyads (274 females; gestational age at birth: 38.89 weeks \pm 2.03). Children born to mothers with both prenatal depression and trait anxiety had higher social-emotional problems (mean difference: 4.66; 95% CI 3.43, 5.90) compared to children born to mothers with no prenatal depression or trait anxiety, each condition alone, or compared to mothers with depression and state anxiety. Additionally, children born to mothers with prenatal maternal depression and trait anxiety had the greatest reduction in mean cognitive scores on the BSID-III ST (mean difference: -1.04; 95% CI -1.99, -0.08).

Conclusions: The observed association between comorbid prenatal maternal depression and chronic anxiety with subsequent child social-emotional and cognitive development underscores the need for targeting mental health support in perinatal women in LMICs to improve long-term child neurobehavioral outcomes.

Strengths and limitations of this study

- The current study included a prospective evaluation of maternal depression and anxiety symptoms during pregnancy and prospective assessment of cognitive and social-emotional outcomes within the same cohort in a large sample of South African mother-children pairs.
- Limitations include a lack of data on maternal mental health assessments postnatally and mother-child dyadic measures, which are potential mediators of the relationship between prenatal maternal depression, prenatal maternal anxiety, and child developmental outcomes.
- This study addresses a significant gap in the literature in research examining the impact of prenatal maternal psychological health on child neurobehavioral development in resource-poor communities.

Keywords: prenatal depression, prenatal anxiety; social-emotional development; cognitive development

Introduction

Decades of research on the early origins of behavior has promoted the concept that the prenatal environment has a profound impact on one's risk for the development of neurodevelopmental or psychiatric disorders^{1 2}. Several prior studies have identified associations between prenatal maternal depression and increased risk for social-emotional problems and decrements in cognitive development. However, the majority of prior research in this domain is from high-income countries (HICs), despite increased reporting of perinatal depression in low and middle income countries (LMICs) including South Africa where an estimated 35% women report prenatal depression^{3 4}. Additionally, despite the comorbidity between depression and anxiety, few prior studies have examined their joint impact on child neurodevelopment.

Several studies in HICs have identified associations between prenatal maternal depression, anxiety, and offspring behavioral, social-emotional, and cognitive development⁵. Specifically, a meta-analysis demonstrated adverse effects of prenatal maternal depression and anxiety on child social-emotional problems, with odds ratios of 1.79 and 1.50 respectively⁶. Prenatal maternal depression and anxiety are also associated with cognitive and language deficits^{7 8}, delayed motor development⁸, emotional and behavior dysregulation⁹⁻¹¹, inattention and hyperactivity¹²⁻¹⁴, and difficult temperament¹⁵. A more recent meta-analysis not only confirmed prior reports, but also found that the effects of perinatal maternal depression extend beyond infancy through adolescence¹⁶.

The developmental origins of health and disease (DOHaD) model posits that maternal psychological distress during pregnancy (e.g. perceived stress, depression, anxiety, post-traumatic stress) may result in changes in hypothalamic pituitary adrenal (HPA) axis function and upregulation of inflammatory processes with downstream effects on offspring perinatal brain

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3 development and behavior¹⁷. Prior research suggests comorbid prenatal maternal depression and
4
5 anxiety may be associated with the greatest increases in maternal HPA-axis activity and
6
7 differential changes in immunologic activity. Specifically, comorbid prenatal maternal
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9 depression and anxiety have been associated with a greater increase in salivary cortisol levels¹⁸,
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11 TH1 secreted cytokines, TH2 secreted cytokines, and TH17 secreted cytokines¹⁹ compared to
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13 either condition alone. Other research suggests cytokine profiles may differ between individuals
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15 with prenatal maternal depression and anxiety¹⁹⁻²¹.
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19 Risk factors may be exacerbated in LMICs such as South Africa, where both poverty and
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21 perinatal mental health disorders are highly prevalent^{22 23}. Specifically, in South Africa maternal
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23 mood disorders have been linked to structural and community stressors associated with markers
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25 of poverty including less than a high school education, lack of social support, alcohol use, family
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27 stress, food insecurity, lack of partner involvement, and intimate partner violence²⁴⁻²⁸. There are
28
29 few prior studies that have examined the impact of prenatal maternal mental health on offspring
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31 social-emotional or cognitive development in South Africa. While the few prior studies reported
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33 significant harmful effects of prenatal maternal stress or perinatal maternal depression, there is
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35 still a significant gap in the literature in research examining the impact of prenatal maternal
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37 psychological health on child neurobehavioral development in resource-poor communities^{24 29 30}.
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39 Additionally, to our knowledge no prior South African studies have examined the joint effect of
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41 prenatal maternal depression and anxiety on child neurobehavioral outcomes. Research
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43 examining the long-term impact of prenatal maternal depression and anxiety on child behavioral
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45 and cognitive outcomes is critical for providing justification to local public health services for
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47 targeting mental health support in perinatal women from underserved communities.
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3 The objective of the current analysis was to determine if prenatal maternal depression and
4 state or trait anxiety were associated with child social-emotional problems or cognitive
5 development at approximately three years of age in a South African cohort from the Western
6 Cape.
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15 **Materials and Methods**

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17 *Participants.* Participants were a subset of infants with available outcome data at age 3 enrolled
18 in the Safe Passage Study conducted by the Prenatal Alcohol and SIDS and Stillbirth (PASS)
19 Network, a multi-center study investigating the role of prenatal exposure in risk for sudden infant
20 death syndrome (SIDS), stillbirth, and fetal alcohol spectrum disorders. Eligibility criteria for the
21 Safe Passage study included the ability to provide informed consent in English or Afrikaans, 16
22 years of age or older at the time of consent, and a gestational age between 6 weeks and 40 weeks
23 at the time of consent based on estimated delivery date³¹. Exclusion Criteria for prenatal
24 maternal enrollment into the Safe Passage study included planned therapeutic abortion, moving
25 out of the catchment area prior to estimated date of delivery, and clinical judgment. Informed
26 consent was obtained for the Safe Passage study and from a parent or legal guardian of each
27 participant for developmental follow-up assessments. Ethical approval was obtained for both
28 time points from the Health Research Ethics Committee of Stellenbosch University and the New
29 York State Psychiatric Institute.
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50 **Maternal Assessments.**

51 *Maternal-infant chart abstraction, demographic, and socioeconomic measures.* Maternal-
52 infant medical charts were abstracted to obtain maternal age at delivery, gestational age at birth,
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3 mode of delivery, and the infant's biological sex. Measures to collect prenatal alcohol, tobacco,
4 and recreational drug exposure have been previously described^{31 32}. Prenatal maternal alcohol
5 and tobacco use behaviors were previously characterized using cluster analysis^{33 34}. Through
6 study specific case report forms, participants indicated demographic and socioeconomic
7 information including race, maternal educational attainment, household crowding (persons per
8 room in household), access to running water inside the house, prenatal care during pregnancy,
9 and marital status.

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19 *Self-reported depression and anxiety measures.* Information regarding maternal mental
20 health during pregnancy was obtained at 20 – 24 weeks' gestation. Depressive symptoms were
21 measured using the Edinburgh Postnatal Depression Scale (EPDS), a depression screening tool
22 developed to specifically assess depressive symptoms in perinatal women where higher scores
23 indicate more severe depressive symptoms^{35 36}. The EPDS is widely used and has been validated
24 in English and Afrikaans in South Africa^{35 37}. Prior studies have used a cut-off score of ≥ 12 or \geq
25 13 to be indicative of major depression within perinatal women living in South Africa^{35 37}.
26 Maternal anxiety symptoms were measured using the State-Trait Anxiety Inventory (STAI)³⁸, an
27 anxiety screening tool to distinguish anxiety symptoms from depressive symptoms which has
28 also been validated in both languages³⁹. The STAI has two subscales, state anxiety which reflects
29 the participant's current state of anxiety when completing the questionnaires and trait anxiety,
30 which is thought to be consistent across time and reflect personality traits. In HICs, the STAI has
31 a cut-off score of ≥ 40 on both the state anxiety and trait anxiety subscales to indicate a threshold
32 for clinical levels of anxiety. Based on these prior studies, we used a cutoff of ≥ 13 to indicate
33 maternal depression, a cutoff of > 40 on the STAI-state subscale to indicate state anxiety, and a
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3 cutoff of > 40 on the STAI-trait subscale to indicate trait anxiety.
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8 Toddler Developmental Assessments.
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10 *Bayley Scales of Infant Development III Screening Test.* The Bayley Scales of Infant
11 Development III Screening Test (BSID-III ST) were designed as a rapid assessment of cognitive,
12 language, and motor functioning in infants and young children in order to determine if a child's
13 development is within normal limits and identify risk for developmental delay. The BSID-III ST
14 has high test-retest reliability: Cognitive (0.85), Receptive Language (0.88), Expressive
15 Language (0.88), Fine Motor (0.82), and Gross Motor (0.86). Although the BSID-III ST does not
16 identify degree of impairment, the cut-off points indicate whether a child shows competence in
17 age-appropriate tasks, evidence of emerging age-appropriate skills, and evidence of being at risk
18 for developmental delay. The BSID has been validated and widely used throughout South
19 Africa^{40 41}.
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33 *Brief Infant Toddler Social Emotional Assessment (BITSEA).* The Brief Infant-Toddler
34 Social and Emotional Assessment (BITSEA) is a 42-item parental report measure of social-
35 emotional development, behavioral problems, and delays in competence⁴². Domains assessed
36 within the BITSEA include: externalizing (activity/impulsivity, aggression/defiance, peer
37 aggression), internalizing (depression/withdrawal, anxiety, separation distress, inhibition to
38 novelty), dysregulation (sleep, negative emotionality, eating, sensory sensitivity), and
39 competence (compliance, attention, imitation/play, mastery motivation, empathy, and pro-social
40 peer relations)⁴². Findings from the BITSEA validation study provide preliminary support for the
41 BITSEA as a reliable and valid brief screener for infant-toddler social-emotional and behavioral
42 problems in addition to delays in competence⁴³. When used in socioeconomically and ethnically
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3 diverse community-based populations, the BITSEA demonstrated excellent test-retest reliability
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5 and good inter-rater agreement between parents⁴².
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10 Statistical Analyses. Using multiple linear regression models, we estimated independent and
11 joint effects of maternal depression and state and trait anxiety on social-emotional problem,
12 social emotional competence, and cognitive development scores. Two, separate four-level
13 categorical prenatal maternal mental health variables were created to assess the impact of
14 prenatal maternal depression, trait anxiety, and state anxiety. We created a prenatal maternal
15 depression and trait anxiety variable with four categories: (1) *No Prenatal Depression or Trait*
16 *Anxiety* (n=199; 33.17%, Reference Category), (2) *Prenatal Depression Only* (106; 17.67%), (3)
17 *Prenatal Trait Anxiety Only* (n=68; 11.33%) and (4) *Prenatal Maternal Depression and Trait*
18 *Anxiety* (n=227; 37.83%) (Table 1). In separate models we additionally examined the
19 independent and joint effects of prenatal maternal depression and state anxiety. We created a
20 prenatal maternal depression and state anxiety variable with four categories: (1) *No Prenatal*
21 *Depression or State Anxiety* (n=248; 41.33%; Reference Category), (2) *Prenatal Depression*
22 *Only* (n=237; 39.50%), (3) *Prenatal State Anxiety Only* (n=19; 3.17%) and (4) *Prenatal*
23 *Maternal Depression and State Anxiety* (n=96; 16%) (Table 1). For each regression model, either
24 *No Prenatal Maternal Depression or Trait Anxiety* or *No Prenatal Maternal Depression and*
25 *State Anxiety* was set as the reference category. Minimally adjusted models included sex,
26 gestational age at birth, and age at follow up as covariates. Fully adjusted models additionally
27 controlled for prenatal maternal alcohol use, prenatal maternal tobacco use, maternal
28 employment status at delivery, maternal educational attainment at delivery, parity, and the
29 household crowding index. We used missing indicator methods and median imputation to
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account for missing categorical and continuous covariate data, respectively (described in Table 1).

All analyses were performed in SAS software version 9.4 (SAS Institute, Cary NC).

Results

Maternal and Child Demographic Characteristics. The participants included in the present analysis consisted of mothers and their infant born between April 2014 and August 2015 from the Western Cape Province of South Africa who participated in a follow-up study to examine social-emotional development and cognitive development at approximately three years of age. A total of n=18 mother-infant dyads were excluded due to missing maternal prenatal mental health data. The final sample consisted of 600 maternal-infant dyads (274 females; gestational age at birth: 38.89 weeks \pm 2.03) (Table 1).

Child Social-Emotional Development. Based on the BITSEA problem scale percentile rank score of 26 or higher, 51% of children (306/600) were classified as having a “possible problem”. Based on the BITSEA competence scale percentile rank score of 15 or lower, 5% (30/600) of children were classified in the “possible deficit/delay range” for social competencies (Table 2). There were no significant sex differences in social-emotional problems on the BITSEA, however girls had significantly higher social-emotional competence compared to boys (mean difference: 0.38, CI: 0.05, 0.71, $p = 0.03$)

Association between Prenatal Maternal Depression, Trait Anxiety, and Child Social-Emotional Development. Compared to children born to mothers with no prenatal depression or trait anxiety, children born to mothers with prenatal depression and trait anxiety had higher social-emotional problems (mean difference: 4.66; 95% CI 3.43, 5.90), followed by prenatal maternal trait anxiety only (mean difference: 3.87; 95% CI 2.07, 5.66), and finally prenatal maternal depression only (mean difference: 2.76; 95% CI 1.23, 4.29) in minimally adjusted

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3 models. These associations remained significant in fully adjusted models where similarly
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5 comorbid prenatal maternal depression and trait anxiety group was associated with the highest
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7 child social-emotional problems (mean difference: 4.33; 95% CI 2.90, 5.67), followed by
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9 prenatal maternal trait anxiety only (mean difference: 3.23; 95% CI 1.19, 5.27), with the smallest
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11 mean difference for prenatal maternal depression only group (mean difference: 2.64; 95% CI
12
13 1.02, 4.27) as compared to the no prenatal depression or trait anxiety group (Figure 1).
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16 Additional significant predictors in the multivariate models were parity of 3 or greater which was
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18 associated with lower social-emotional problems (mean difference: -3.02, 95% CI -4.63, -1.40)
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20 and low continuous smoking during pregnancy which was associated with higher social-
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22 emotional problems (mean difference: 1.39, 95% CI 0.039, 2.74). There were no significant
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24 associations between prenatal maternal depression, trait anxiety, and child social-emotional
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26 competence.
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31 *Association between Prenatal Maternal Depression, State Anxiety, and Child Social-*
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33 *Emotional Development.* Compared to children born to mothers with no prenatal depression or
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35 state anxiety, children born to mothers with comorbid prenatal depression and state anxiety had
36
37 higher social-emotional problems (mean difference: 4.29; 95% CI 2.73, 5.84). Children born to
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39 mothers with prenatal depression only also had higher social-emotional problems compared to
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41 mothers with no prenatal depression or state anxiety (mean difference: 2.71; 95% CI 1.51, 3.88).
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43 These associations remained significant in fully adjusted models (prenatal depression and state
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45 anxiety: 3.90 mean increase (95% CI 2.19, 5.60); prenatal depression only: 2.58 mean increase
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47 (95% CI 1.34, 3.82)) (Figure 1). Additional significant predictors in the multivariate models
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49 were parity of 3 or greater which was associated with lower social-emotional problems (mean
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51 difference: -3.22, 95% CI -4.86, -1.58), low continuous smoking during pregnancy which was
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3 associated with higher social-emotional problems (mean difference: 1.44; 95% CI 0.075, 2.81),
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5 and finally less than a high school education (some primary school only) which was associated
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7 with higher social-emotional problems (mean difference: 3.47; 95% CI 0.248, 6.70). However,
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9 there was no significant association between prenatal state anxiety only and child social-
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11 emotional problems on the BITSEA. There were also no significant associations between
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13 prenatal maternal depression, state anxiety, and social-emotional competence.
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17 *Child Cognitive, Language, and Motor Development.* Based on normative cognitive
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19 cutoff scores defined by the BSID-III ST, 4% of children (24/600) were classified as at-risk
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21 (Table 2). Risk classification percentages were similar across all subdomains, expressive
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23 language: 4% , receptive language: 6%, gross motor: 4%, and fine motor: 3%. There were no
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25 significant sex differences in child cognitive scores.
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29 *Association between Prenatal Maternal Depression, Trait Anxiety, and Child Cognitive,*
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31 *Language, and Motor Development.* Compared to children born to mothers with no prenatal
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33 depression or trait anxiety, children born to mothers with comorbid prenatal depression and trait
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35 anxiety had lower cognitive scores on the BSID-III ST (mean difference: -1.04; 95% CI -1.99, -
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37 0.08). Results remained significant in the fully adjusted model (mean difference: -1.11; 95% CI -
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39 2.13, -0.09) (Figure 2) and in posthoc analyses where we additionally controlled for language of
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41 administration for the BSID-III ST (mean difference: -0.51, 95% CI -0.99, -0.042). Children who
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43 were assessed on the BSID-III ST in Afrikaans (mean difference: -1.00, 95% CI -1.48, -0.52) or
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45 who were assessed in mixed English and Afrikaans (mean difference: -1.30, 95% CI -2.07, -
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47 0.54) has significantly lower cognitive scores compared to children assessed in English. Low
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49 continuous prenatal maternal alcohol use was also associated with lower cognitive scores (mean
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51 difference: -1.30; 95% CI -2.36, -0.24).
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3 *Association between Prenatal Maternal Depression, State Anxiety, and Child Cognitive,*
4 *Language, and Motor Development.* Compared to children born to mothers with neither prenatal
5 depression nor trait anxiety, there was no significant association between cognitive scores for
6 children born to mothers with prenatal depression only, prenatal trait anxiety only, or combined
7 prenatal depression and trait anxiety in either the minimally or fully adjusted models.
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17 **Discussion**

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19 In summary, we found the greatest increase in child social-emotional problems in
20 children born to women with comorbid prenatal depression and trait anxiety compared to women
21 with no prenatal depression or trait anxiety, prenatal depression alone, or prenatal trait anxiety
22 alone. We additionally found a significant association between comorbid prenatal maternal
23 depression and state anxiety on higher child social-emotional problems; however, we found no
24 association between prenatal maternal state anxiety in the absence of prenatal maternal
25 depression on child social-emotional problems. Finally, we reported children born to mothers
26 with prenatal maternal depression and trait anxiety had lower cognitive scores on the BSID-III
27 ST, but we did not find an association between prenatal maternal depression alone on cognitive
28 outcomes at 3-years of age.
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42 Our finding linking prenatal maternal depression and anxiety to social-emotional risk
43 parallels two recent South African studies linking increased prenatal maternal stressors to higher
44 behavioral problems in children with an odds ratio of 2.52, but not before 4 years of age²⁹ and
45 increased perinatal depression to aggressive behaviors at 60 months of age²⁴. Our findings are
46 also largely consistent with a recent meta-analysis of studies predominately conducted in HICs,
47 which found prenatal maternal depression and anxiety were associated with higher social-
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3 emotional problems in offspring with larger effect sizes for prenatal maternal depression (OR
4 1.79; 95% CI 1.61 - 1.99) compared to prenatal maternal anxiety (OR 1.50, 95% CI, 1.36 -
5 1.64)⁶. We found the greatest increase in child social-emotional problems in children born to
6 women with comorbid prenatal depression and trait anxiety and no effect of prenatal maternal
7 state anxiety in the absence of prenatal maternal depression on child social-emotional problems.
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9 Our results are suggestive that chronic anxiety measured via trait anxiety may be more predictive
10 of child social-emotional outcomes than a single measurement of concurrent anxiety during
11 pregnancy.
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21 A prior meta-analysis⁶ also found stronger effects of prenatal maternal depression and
22 anxiety on child social-emotional outcomes when sociodemographic risk factors such as low-
23 income, lower levels of parental education, or single family households, were highest⁶. Similarly,
24 we found that lower levels of maternal education, low continuous tobacco use during pregnancy,
25 and low continuous alcohol use during pregnancy were associated with higher social-emotional
26 problems in children at three years of age. Intriguingly, maternal parity of 3 or greater was
27 protective and associated with lower social-emotional problems which may be due to reduced
28 depression and anxiety levels in women with higher parity, changes in the perception of their
29 child's behavior due to having multiple children, or additional social opportunities during sibling
30 interactions^{44 45}.
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44 The Drakenstein Child Health Study based in the Western Cape found approximately
45 50% of the overall sample (369/731) were categorized as having cognitive delay at two years of
46 age based on cutoffs defined by United States (US) normative data³⁰. Better cognitive outcomes
47 were associated with higher maternal education, older child age, a primigravid mother, and
48 higher socioeconomic status whereas prenatal maternal depression was associated with a 1.03
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3 SD (95% CI -1.94 to -0.12) reduction in cognitive scores on the Bayley Scales of Infant and
4 Toddler Development at two years of age³⁰. Similar to the Drakenstein Child Health Study³⁰, we
5 found children born to mothers with prenatal maternal depression and trait anxiety had lower
6 cognitive scores on the BSID-III ST compared to the no prenatal maternal depression or trait
7 anxiety group. In contrast, we did not find an association between prenatal maternal depression
8 alone on cognitive outcomes at 3-years of age. However, since we did not utilize the full BSID-
9 III and only administered the BSID-III ST, it is difficult to directly compare our results to The
10 Drakenstein Child Health study findings. Moreover, both studies relied on US normative data to
11 define cutoff scores.
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24 More recently, a large home-visiting intervention study based in Cape Town examined
25 the effect of prenatal maternal depression only, postnatal maternal depression only (birth – 60
26 months), or recurrent pre- and postnatal maternal depression. This study also accounted for
27 several other risk factors including intimate partner violence, HIV status, and alcohol use on
28 child social behaviors, language skills, and cognitive development. No associations were found
29 between maternal depression at any time point with children's language or cognitive
30 development at 36 or 60 months of age²⁴. However, children of never depressed mothers had
31 lower aggressive behaviors on the Child Behavior Checklist at 60 months of age than children of
32 mothers with postnatal depression only or perinatal depression²⁴.
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44 There are several biological mechanisms which can explain prior studies and our current
45 findings linking prenatal maternal depression and anxiety with child social-emotional behaviors
46 and cognitive development such as increased prenatal maternal inflammation, increased cortisol
47 production, and/or epigenetic changes⁴⁶⁻⁵⁵. Pregnancy is associated with changes in inflammatory
48 processes and increased placental cortisol production with reduced maternal HPA axis sensitivity
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3 to stress^{46,47}. However, prenatal maternal depression may upregulate inflammatory processes
4 and/or cortisol production. Additionally, prior research found women with comorbid depression
5 and anxiety have the greatest increases in salivary cortisol levels¹⁸. Maternal cortisol can cross
6 the placenta resulting in increased inflammation^{46,47} and/or affect the developmental of limbic
7 regions, which are associated with social and emotional processes⁵⁶. In animal models, increased
8 proinflammatory proteins have been associated with widespread changes in perinatal brain
9 development such as with volume reductions in gray and white matter, decreased density of
10 GABAergic neurons, reduced synaptic pruning, and network dysfunction with potential
11 downstream effects on neurobehavioral development⁴⁸⁻⁵⁵. Other studies examining the
12 intergenerational transmission of trauma have demonstrated transgenerational epigenetic changes
13 in animal models⁵⁷. Taken together, prior research suggests multiple overlapping pathways by
14 which prenatal maternal mood can affect offspring brain-behavioral development.

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17 While we report an association of prenatal maternal depression and anxiety with child
18 social-emotional and cognitive development from a prospective cohort study with a fairly large
19 sample of participants, there are several methodological and contextual limitations within the
20 current study that are worth noting. First, it is important to note that the reliance on maternal-
21 report measures to characterize child social-emotional development is a limitation in the majority
22 of research to date, including the present study. The reliance on maternal reporting of child
23 social-emotional development may be influenced by factors such as maternal mood or education.
24 An additional limitation was the use of the BSID-III screening test in the current study to
25 measure cognitive development, which is based on US normative data. Future studies should
26 consider objective measures of child social-emotional development through observational or
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3 behavioral coding paradigms in addition to utilizing objective cognitive developmental
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5 assessments of with normative data in South African children.
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8 There are also several unmeasured contextual factors which could affect our findings. For
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10 example, although prenatal maternal and child nutrition are known to affect child
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12 neurobehavioral development, we lacked measures of prenatal maternal nutrition, prenatal
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14 maternal micronutrient deficiencies, prenatal and postnatal household food insecurity, and
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16 information regarding child nutrition. Additionally, prior studies have emphasized the
17
18 importance of measuring childhood trauma, maternal stress, and social support within
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20 communities with several heterogeneous risk factors³, these measures were not collected as part
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22 of the original NIH Safe Passage Study or our recent follow-up study. Therefore, we could not
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24 examine their effects or consider maternal social support as a potential moderator of resilient
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26 neurodevelopmental outcomes. There is also robust literature examining both postpartum
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28 depression (PPD) and the early mother-infant relation in shaping child outcomes. Two prior
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30 studies in South Africa demonstrated maternal intrusiveness and coerciveness mediated the
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32 association between maternal PPD and early childhood attachment^{58 59}. In the current study, we
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34 did not collect data postnatally between birth and three years of age. Additionally, we did not
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36 collect postnatal information on maternal depression, anxiety, or stress. Therefore, due to this
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38 methodological limitation we cannot draw conclusions regarding the combined effect of the pre-
39
40 and postnatal environment on child neurodevelopmental outcomes, nor can we assess potential
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42 interaction effects between pre- and postnatal maternal mood on child social-emotional and
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44 cognitive outcomes. Finally, our results may not generalize to all South African populations
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46 where HIV rates can be as high as 35% since our cohort only included one woman with HIV.
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Strengths of the current analyses include our large sample size, evaluation of both cognitive and

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3 social-emotional outcomes within the same cohort, finally the detailed prospective collection of
4 both depression and anxiety symptoms during pregnancy³¹ in addition to other potential
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6 confounders.
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10 Our results suggest comorbid prenatal maternal depression and chronic anxiety have a
11 greater impact on child social-emotional and cognitive development than either condition alone
12 or than comorbid prenatal maternal depression and transitory anxiety during pregnancy. These
13 findings are supported by a robust literature within the DOHaD framework linking perturbations
14 in the gestational environment to later neurodevelopmental or psychiatric sequelae. Our results
15 also lend support for future intervention studies aimed at perinatal mental health interventions
16 targeting maternal depressive and anxiety symptoms to improve long-term child social-emotional
17 and cognitive developmental outcomes in low-resource communities.
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Table 1 - Sociodemographic characteristics		
	Mean \pm SD or N (%)	N and Percent Missing (%)
Maternal Characteristics		
Maternal Age (years)	25.26 \pm 5.91	0 (0%)
Maternal Body Mass Index (BMI)		0 (0%)
	BMI <18.5 (kg/m ²)	62 (10.33%)
	BMI 18.5-25 (kg/m ²)	282 (47%)
	BMI 25-30 (kg/m ²)	132 (22%)
	BMI >30 (kg/m ²)	124 (20.67%)
Parity		0 (0%)
	Parity <1	218 (36.33%)
	Parity =1	196 (32.67%)
	Parity =2	103 (17.17%)
	Parity \geq 3	83 (13.83%)
Antenatal care visits		0 (0%)
	antenatal care visit <3	49 (8.17%)
	antenatal care visit 3-6	389 (64.83%)
	antenatal care visit >6	162 (27%)
Cesarean Section	106 (17.70%)	1 (0.1%)
Education		0 (0%)
	Some primary school	43 (7.167%)
	Some high school	405 (67.57%)
	Completed high school	119 (19.83%)
	Beyond high school	33 (5.5%)
Married	290 (48.33%)	0 (0%)
Employed	172 (28.67%)	0 (0%)
Adjusted Household Crowding	1.56 \pm 0.72	2 (0.33%)
Depression (Edinburgh \geq 13)	333 (55%)	0 (0%)
Anxiety (State-Trait Anxiety Inventory \geq 40)	115 (19.17%)	0 (0%)
Maternal Prenatal Alcohol Use Cluster Groups		0 (0%)
Non drinking group: 0 standard drinks/trimester	245 (46.93%)	
Moderate-high continuous drinking group:	122 (23.37%)	
	Standard drinks in Trimester 1	27 \pm 39
	Standard drinks in Trimester 2	17 \pm 25
	Standard drinks in Trimester 3	9.4 \pm 15
Binge drinking events (\geq 4 drinks/day) Trimester 1	2.7 \pm 4	

Binge drinking events (≥ 4 drinks/day) Trimester 2	1.7 \pm 2.8	
Binge drinking events (≥ 4 drinks/day) Trimester 3	0.89 \pm 1.7	
Low continuous drinking	26 (4.98%)	
Standard drinks in Trimester 1	1.4 \pm 2.5	
Standard drinks in Trimester 2	4 \pm 2.8	
Standard drinks in Trimester 3	0.62 \pm 1.1	
Binge drinking events (≥ 4 drinks/day) Trimester 1	0.067 \pm 0.25	
Binge drinking events (≥ 4 drinks/day) Trimester 2	0.30 \pm 0.46	
Binge drinking events (≥ 4 drinks/day) Trimester 3	0 \pm 0	
Quit early drinking	129 (24.71%)	
Standard drinks in Trimester 1	8.5 \pm 6.5	
Standard drinks in Trimester 2	0.31 \pm 0.87	
Standard drinks in Trimester 3	0.056 \pm 0.31	
Binge drinking events (≥ 4 drinks/day) Trimester 1	0.84 \pm 0.82	
Binge drinking events (≥ 4 drinks/day) Trimester 2	0 \pm 0	
Binge drinking events (≥ 4 drinks/day) Trimester 3	0 \pm 0	
Maternal Prenatal Tobacco Use		2 (0.33%)
Non smoking (0 cigarettes/trimester)	227 (37.97%)	
Moderate-high continuous smoking	132 (22.07%)	
Average Cigarettes in Trimester 1	45 \pm 20	
Average Cigarettes in Trimester 2	50 \pm 27	
Average Cigarettes in Trimester 3	48 \pm 25	
Low continuous smoking	222 (37.12%)	
Average Cigarettes in Trimester 1	16 \pm 9.4	
Average Cigarettes in Trimester 2	16 \pm 9.7	
Average Cigarettes in Trimester 3	16 \pm 10	
Quit early smoking	17 (2.84%)	
Average Cigarettes in Trimester 1	11 \pm 7.5	
Average Cigarettes in Trimester 2	0.15 \pm 0.32	
Average Cigarettes in Trimester 3	0.079 \pm 0.11	
Raw Maternal Edinburgh Score	12.99 \pm 5.73	0 (0%)
Raw Maternal State Anxiety Score	31.23 \pm 10.24	0 (0%)
Raw Maternal Trait Anxiety Score	40.63 \pm 10.63	0 (0%)
Depression - Trait Anxiety Groups		0 (0%)
No depression or trait anxiety	199 (33.17%)	
Depression alone	106 (17.67%)	
Trait anxiety alone	68 (11.33%)	
Depression and trait anxiety	227 (37.83%)	
Depression - State Anxiety Groups		0 (0%)
No depression or state anxiety	248 (41.33%)	

HIV status	Depression alone	237 (39.50%)	
	State anxiety alone	19 (3.17%)	
	Depression and state anxiety	96 (16%)	
	Tested for HIV	600 (100%)	
	HIV positive	1 (0.1%)	
Infant Characteristics			
Infant Sex			0 (0%)
	Male	326 (54.33%)	
	Female	274 (45.67%)	
Gestational age at birth (weeks)		38.89 ± 2.03	0 (0%)
Infant Birth weight (grams)		2980.65 ± 564.65	2 (0.33%)
Follow-up age (months)		38.29 ± 2.96	0 (0%)
Adjusted follow-up age (months)		38.14 ± 0.016	0 (0%)

Table 2. Neurodevelopmental Outcome Raw Scores and At-risk Groups

BSID-III Screening Test Language of Administration			
	English Only	177 (30%)	
	Afrikaans Only	360 (62%)	
	Mixed English and Afrikaans	48 (8%)	
BSID-III Screening Test Scores			
	Gross motor	25.47 ± 4.54	
	Fine motor	23.55 ± 4.08	
	Cognitive	27.77 ± 4.99	
	Problem solving	13.40 ± 6.77	
	Receptive language	21.69 ± 5.10	
	Expressive language	21.27 ± 3.78	
At-Risk Categories			
	Gross motor	21 (4%)	
	Fine motor	18 (3%)	
	Cognitive	24 (4%)	
	Receptive language	33 (6%)	
	Expressive language	25 (4%)	
Brief Infant Toddler Social-Emotional Assessment (BITSEA)			
	Social Emotional Problem	13.40 ± 6.77	
	Competence	19.56 ± 2.07	
At-Risk Categories			
	Social Emotional Problems	306 (51%)	

Social-Emotional Competence	30 (5%)
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Figure Legends

Figure 1. Association between prenatal maternal depression, prenatal maternal anxiety, and child social-emotional problems measured by the BITSEA. Each line plot depicts the mean difference and their confidence interval for child social-emotional problems (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

Figure 2. Association between prenatal maternal depression, prenatal maternal anxiety, and child cognitive development measured by the BSID-III Screening Test. Each line plot depicts the mean difference and their confidence interval for child cognitive development (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

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49 **Contributors:** WPF and HJO acquired funding for and designed the work. LCS, AS, NHB, ML,
50 YR, PES, HJO, and WPF conceptualized the work. MP, PES, CDP, and HJO acquired the data.
51
52
53
54 LCS, NHB, and WPF led in data collection oversight and quality control. AS, LCS, and YR
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2
3 analyzed the data. All authors contributed to the interpretation of data and drafting the work and
4
5 revising it critically for important intellectual content. All authors approved the final manuscript
6
7 and agree to be accountable for all aspects of the work.
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10
11
12 **Acknowledgements:** We would like to acknowledge Lucy Brink, J. David Nugent, and Daianna
13
14 Rodriguez for their database and administrative support. We would also like to thank all of the
15
16 families who participated in this research study for making this work possible.
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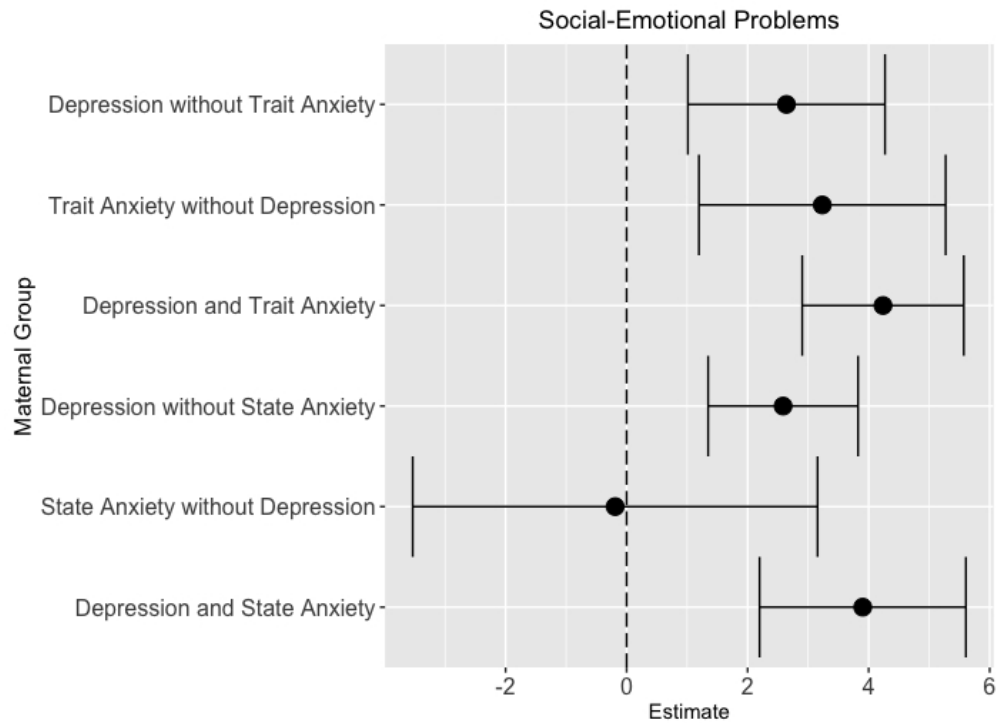
20 21 **Ethics statements**

22 **Patient consent for publication**

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30 **Ethics approval**

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33 Ethics approval was received from the Institutional Review Boards and ethics review committees
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35 at Stellenbosch University (N16-08-101 and N06-10-210) and the New York State Psychiatric
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37 Institute (5338). All participants provided informed written consent at both time points (prenatal
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39 and postnatal) before inclusion in the study.
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Figure 1. Association between prenatal maternal depression, prenatal maternal anxiety, and child social-emotional problems measured by the BITSEA. Each line plot depicts the mean difference and their confidence interval for child social-emotional problems (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

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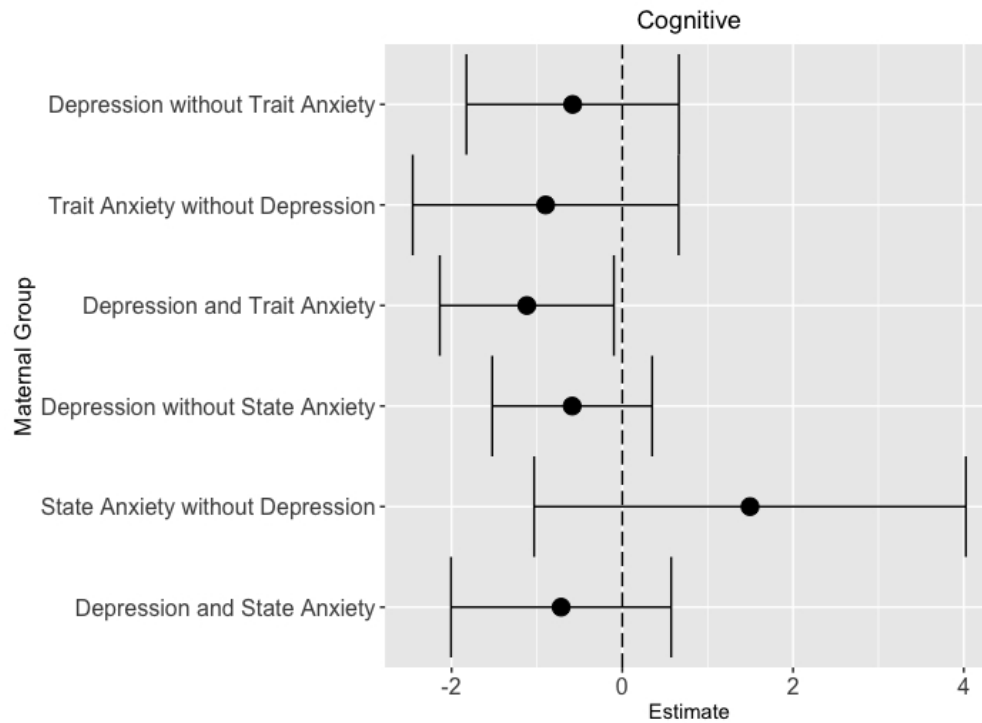


Figure 2. . Association between prenatal maternal depression, prenatal maternal anxiety, and child cognitive development measured by the BSID-III Screening Test. Each line plot depicts the mean difference and their confidence interval for child cognitive development (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	2 3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7 - 9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 - 9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7 - 9 N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9 - 10
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 - 10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9 - 10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	9 - 10 9 - 10 10 10 N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11 11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9, 11 - 13 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11 - 13
2			(b) Report category boundaries when continuous variables were categorized	N/A
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11 - 13
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11	Discussion			
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13	Key results	18	Summarise key results with reference to study objectives	14
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
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16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
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19	Generalisability	21	Discuss the generalisability (external validity) of the study results	17
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21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Association of Maternal Depression and Anxiety with Toddler Social-Emotional and Cognitive Development in South Africa: A prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058135.R2
Article Type:	Original research
Date Submitted by the Author:	17-Mar-2022
Complete List of Authors:	Shuffrey, Lauren; Columbia University Irving Medical Center, Psychiatry; New York State Psychiatric Institute, Division of Developmental Neuroscience Sania, Ayesha; Columbia University Irving Medical Center, Psychiatry; New York State Psychiatric Institute, Division of Developmental Neuroscience Brito, Natalie; New York University, Department of Applied Psychology Potter, Mandy; Stellenbosch University Faculty of Medicine and Health Sciences, Obstetrics and Gynaecology Springer, Priscilla; Stellenbosch University, Paediatrics and Child Health Lucchini, Maristella ; Columbia University Irving Medical Center, Psychiatry; New York State Psychiatric Institute, Neuroscience Rayport, Yael; Columbia University Irving Medical Center, Department of Psychiatry; New York State Psychiatric Institute, Neuroscience Du Plessis, Carlie; Stellenbosch University Faculty of Medicine and Health Sciences, Department of Obstetrics and Gynaecology Odendaal, H. J.; Stellenbosch University Faculty of Medicine and Health Sciences, Obstetrics & Gynaecology Fifer, William; Columbia University Irving Medical Center, Psychiatry; New York State Psychiatric Institute, Neuroscience
Primary Subject Heading:	Global health
Secondary Subject Heading:	Mental health, Paediatrics
Keywords:	Community child health < PAEDIATRICS, Depression & mood disorders < PSYCHIATRY, Anxiety disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY

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Title: Association of Maternal Depression and Anxiety with Toddler Social-Emotional and Cognitive Development in South Africa: A prospective cohort study

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Financial Support: This research was supported by the Bill and Melinda Gates Foundation (WPF) and grants U01HD055154, U01HD045935, U01HD055155, and U01HD045991 issued by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and grant U01AA016501 issued by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Dr. Lauren Shuffrey is supported by K99HD103910 issued by the Eunice Kennedy Shriver National Institute Of Child Health & Human Development. Dr. Ayesha Sania is supported by UH3OD023279-05S1, re-entry supplement from Office of the Director, NIH, and Office of Research on Women Health (ORWH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests: The authors have no competing interests to declare.

Data availability: Data are available upon reasonable request.

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Abstract:

Objective: A robust literature has identified associations between prenatal maternal depression and adverse child social-emotional and cognitive outcomes. The majority of prior research is from high-income countries despite increased reporting of perinatal depression in low and middle income countries (LMICs). Additionally, despite the comorbidity between depression and anxiety, few prior studies have examined their joint impact on child neurodevelopment. The objective of the current analysis was to examine associations between prenatal maternal depression and anxiety with child social-emotional and cognitive development in a cohort from the Western Cape Province of South Africa.

Design: Prenatal maternal depression and anxiety were measured using the Edinburgh Postnatal Depression Scale (EPDS) and the State-Trait Anxiety Scale (STAI) at 20 – 24 weeks' gestation. Child neurobehavior was assessed at age 3 using the Brief Infant Toddler Social Emotional Assessment (BITSEA) and the Bayley Scales of Infant Development Screening Test (BSID-III ST). We used linear regression models to examine the independent and joint association between prenatal maternal depression, anxiety, and child developmental outcomes.

Results: Participants consisted of 600 maternal-infant dyads (274 females; gestational age at birth: 38.89 weeks \pm 2.03). Children born to mothers with both prenatal depression and trait anxiety had higher social-emotional problems (mean difference: 4.66; 95% CI 3.43, 5.90) compared to children born to mothers with no prenatal depression or trait anxiety, each condition alone, or compared to mothers with depression and state anxiety. Additionally, children born to mothers with prenatal maternal depression and trait anxiety had the greatest reduction in mean cognitive scores on the BSID-III ST (mean difference: -1.04; 95% CI -1.99, -0.08).

Conclusions: The observed association between comorbid prenatal maternal depression and chronic anxiety with subsequent child social-emotional and cognitive development underscores the need for targeting mental health support in perinatal women in LMICs to improve long-term child neurobehavioral outcomes.

Strengths and limitations of this study

- The current study included a prospective evaluation of maternal depression and anxiety symptoms during pregnancy and prospective assessment of cognitive and social-emotional outcomes within the same cohort in a large sample of South African mother-children pairs.
- Limitations include a lack of data on maternal mental health assessments postnatally and mother-child dyadic measures, which are potential mediators of the relationship between prenatal maternal depression, prenatal maternal anxiety, and child developmental outcomes.
- This study addresses a significant gap in the literature in research examining the impact of prenatal maternal psychological health on child neurobehavioral development in resource-poor communities.

Keywords: prenatal depression, prenatal anxiety; social-emotional development; cognitive development

Introduction

Decades of research on the early origins of behavior has promoted the concept that the prenatal environment has a profound impact on one's risk for the development of neurodevelopmental or psychiatric disorders^{1 2}. Several prior studies have identified associations between prenatal maternal depression and increased risk for social-emotional problems and decrements in cognitive development. However, the majority of prior research in this domain is from high-income countries (HICs), despite increased reporting of perinatal depression in low and middle income countries (LMICs) including South Africa where an estimated 35% women report prenatal depression^{3 4}. Additionally, despite the comorbidity between depression and anxiety, few prior studies have examined their joint impact on child neurodevelopment.

Several studies in HICs have identified associations between prenatal maternal depression, anxiety, and offspring behavioral, social-emotional, and cognitive development⁵. Specifically, a meta-analysis demonstrated adverse effects of prenatal maternal depression and anxiety on child social-emotional problems, with odds ratios of 1.79 and 1.50 respectively⁶. Prenatal maternal depression and anxiety are also associated with cognitive and language deficits^{7 8}, delayed motor development⁸, emotional and behavior dysregulation⁹⁻¹¹, inattention and hyperactivity¹²⁻¹⁴, and difficult temperament¹⁵. A more recent meta-analysis not only confirmed prior reports, but also found that the effects of perinatal maternal depression extend beyond infancy through adolescence¹⁶.

The developmental origins of health and disease (DOHaD) model posits that maternal psychological distress during pregnancy (e.g. perceived stress, depression, anxiety, post-traumatic stress) may result in changes in hypothalamic pituitary adrenal (HPA) axis function and upregulation of inflammatory processes with downstream effects on offspring perinatal brain

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3 development and behavior¹⁷. Prior research suggests comorbid prenatal maternal depression and
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5 anxiety may be associated with the greatest increases in maternal HPA-axis activity and
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7 differential changes in immunologic activity. Specifically, comorbid prenatal maternal
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9 depression and anxiety have been associated with a greater increase in salivary cortisol levels¹⁸,
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11 TH1 secreted cytokines, TH2 secreted cytokines, and TH17 secreted cytokines¹⁹ compared to
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13 either condition alone. Other research suggests cytokine profiles may differ between individuals
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15 with prenatal maternal depression and anxiety¹⁹⁻²¹.
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19 Risk factors may be exacerbated in LMICs such as South Africa, where both poverty and
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21 perinatal mental health disorders are highly prevalent^{22 23}. Specifically, in South Africa maternal
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23 mood disorders have been linked to structural and community stressors associated with markers
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25 of poverty including less than a high school education, lack of social support, alcohol use, family
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27 stress, food insecurity, lack of partner involvement, and intimate partner violence²⁴⁻²⁸. There are
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29 few prior studies that have examined the impact of prenatal maternal mental health on offspring
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31 social-emotional or cognitive development in South Africa. While the few prior studies reported
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33 significant harmful effects of prenatal maternal stress or perinatal maternal depression, there is
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35 still a significant gap in the literature in research examining the impact of prenatal maternal
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37 psychological health on child neurobehavioral development in resource-poor communities^{24 29 30}.
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39 Additionally, to our knowledge no prior South African studies have examined the joint effect of
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41 prenatal maternal depression and anxiety on child neurobehavioral outcomes. Research
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43 examining the long-term impact of prenatal maternal depression and anxiety on child behavioral
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45 and cognitive outcomes is critical for providing justification to local public health services for
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47 targeting mental health support in perinatal women from underserved communities.
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3 The objective of the current analysis was to determine if prenatal maternal depression and
4 state or trait anxiety were associated with child social-emotional problems or cognitive
5 development at approximately three years of age in a South African cohort from the Western
6 Cape.
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15 **Materials and Methods**

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17 *Participants.* Participants were a subset of infants with available outcome data at age 3 enrolled
18 in the Safe Passage Study conducted by the Prenatal Alcohol and SIDS and Stillbirth (PASS)
19 Network, a multi-center study investigating the role of prenatal exposure in risk for sudden infant
20 death syndrome (SIDS), stillbirth, and fetal alcohol spectrum disorders. Eligibility criteria for the
21 Safe Passage study included the ability to provide informed consent in English or Afrikaans, 16
22 years of age or older at the time of consent, and a gestational age between 6 weeks and 40 weeks
23 at the time of consent based on estimated delivery date³¹. Exclusion Criteria for prenatal
24 maternal enrollment into the Safe Passage study included planned therapeutic abortion, moving
25 out of the catchment area prior to estimated date of delivery, and clinical judgment. Informed
26 consent was obtained for the Safe Passage study and from a parent or legal guardian of each
27 participant for developmental follow-up assessments. Ethical approval was obtained for both
28 time points from the Health Research Ethics Committee of Stellenbosch University and the New
29 York State Psychiatric Institute.
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50 **Maternal Assessments.**

51 *Maternal-infant chart abstraction, demographic, and socioeconomic measures.* Maternal-
52 infant medical charts were abstracted to obtain maternal age at delivery, gestational age at birth,
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3 mode of delivery, and the infant's biological sex. Measures to collect prenatal alcohol, tobacco,
4 and recreational drug exposure have been previously described^{31 32}. Prenatal maternal alcohol
5 and tobacco use behaviors were previously characterized using cluster analysis^{33 34}. Through
6 study specific case report forms, participants indicated demographic and socioeconomic
7 information including race, maternal educational attainment, household crowding (persons per
8 room in household), access to running water inside the house, prenatal care during pregnancy,
9 and marital status.

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19 *Self-reported depression and anxiety measures.* Information regarding maternal mental
20 health during pregnancy was obtained at 20 – 24 weeks' gestation. Depressive symptoms were
21 measured using the Edinburgh Postnatal Depression Scale (EPDS), a depression screening tool
22 developed to specifically assess depressive symptoms in perinatal women where higher scores
23 indicate more severe depressive symptoms^{35 36}. The EPDS is widely used and has been validated
24 in English and Afrikaans in South Africa^{35 37}. Prior studies have used a cut-off score of ≥ 12 or \geq
25 13 to be indicative of major depression within perinatal women living in South Africa^{35 37}.
26 Maternal anxiety symptoms were measured using the State-Trait Anxiety Inventory (STAI)³⁸, an
27 anxiety screening tool to distinguish anxiety symptoms from depressive symptoms which has
28 also been validated in both languages³⁹. The STAI has two subscales, state anxiety which reflects
29 the participant's current state of anxiety when completing the questionnaires and trait anxiety,
30 which is thought to be consistent across time and reflect personality traits. In HICs, the STAI has
31 a cut-off score of ≥ 40 on both the state anxiety and trait anxiety subscales to indicate a threshold
32 for clinical levels of anxiety. Based on these prior studies, we used a cutoff of ≥ 13 to indicate
33 maternal depression, a cutoff of > 40 on the STAI-state subscale to indicate state anxiety, and a
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3 cutoff of > 40 on the STAI-trait subscale to indicate trait anxiety.
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8 Toddler Developmental Assessments.
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10 *Bayley Scales of Infant Development III Screening Test.* The Bayley Scales of Infant
11 Development III Screening Test (BSID-III ST) were designed as a rapid assessment of cognitive,
12 language, and motor functioning in infants and young children in order to determine if a child's
13 development is within normal limits and identify risk for developmental delay. The BSID-III ST
14 has high test-retest reliability: Cognitive (0.85), Receptive Language (0.88), Expressive
15 Language (0.88), Fine Motor (0.82), and Gross Motor (0.86). Although the BSID-III ST does not
16 identify degree of impairment, the cut-off points indicate whether a child shows competence in
17 age-appropriate tasks, evidence of emerging age-appropriate skills, and evidence of being at risk
18 for developmental delay. The BSID has been validated and widely used throughout South
19 Africa^{40 41}.
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33 *Brief Infant Toddler Social Emotional Assessment (BITSEA).* The Brief Infant-Toddler
34 Social and Emotional Assessment (BITSEA) is a 42-item parental report measure of social-
35 emotional development, behavioral problems, and delays in competence⁴². Domains assessed
36 within the BITSEA include: externalizing (activity/impulsivity, aggression/defiance, peer
37 aggression), internalizing (depression/withdrawal, anxiety, separation distress, inhibition to
38 novelty), dysregulation (sleep, negative emotionality, eating, sensory sensitivity), and
39 competence (compliance, attention, imitation/play, mastery motivation, empathy, and pro-social
40 peer relations)⁴². Findings from the BITSEA validation study provide preliminary support for the
41 BITSEA as a reliable and valid brief screener for infant-toddler social-emotional and behavioral
42 problems in addition to delays in competence⁴³. When used in socioeconomically and ethnically
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3 diverse community-based populations, the BITSEA demonstrated excellent test-retest reliability
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5 and good inter-rater agreement between parents⁴².
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10 Statistical Analyses. Using multiple linear regression models, we estimated independent and
11 joint effects of maternal depression and state and trait anxiety on social-emotional problem,
12 social emotional competence, and cognitive development scores. Two, separate four-level
13 categorical prenatal maternal mental health variables were created to assess the impact of
14 prenatal maternal depression, trait anxiety, and state anxiety. We created a prenatal maternal
15 depression and trait anxiety variable with four categories: (1) *No Prenatal Depression or Trait*
16 *Anxiety* (n=199; 33.17%, Reference Category), (2) *Prenatal Depression Only* (106; 17.67%), (3)
17 *Prenatal Trait Anxiety Only* (n=68; 11.33%) and (4) *Prenatal Maternal Depression and Trait*
18 *Anxiety* (n=227; 37.83%) (Table 1). In separate models we additionally examined the
19 independent and joint effects of prenatal maternal depression and state anxiety. We created a
20 prenatal maternal depression and state anxiety variable with four categories: (1) *No Prenatal*
21 *Depression or State Anxiety* (n=248; 41.33%; Reference Category), (2) *Prenatal Depression*
22 *Only* (n=237; 39.50%), (3) *Prenatal State Anxiety Only* (n=19; 3.17%) and (4) *Prenatal*
23 *Maternal Depression and State Anxiety* (n=96; 16%) (Table 1). For each regression model, either
24 *No Prenatal Maternal Depression or Trait Anxiety* or *No Prenatal Maternal Depression and*
25 *State Anxiety* was set as the reference category. Minimally adjusted models included sex,
26 gestational age at birth, and age at follow up as covariates. Fully adjusted models additionally
27 controlled for prenatal maternal alcohol use, prenatal maternal tobacco use, maternal
28 employment status at delivery, maternal educational attainment at delivery, parity, and the
29 household crowding index. We used missing indicator methods and median imputation to
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account for missing categorical and continuous covariate data, respectively (described in Table 1).

All analyses were performed in SAS software version 9.4 (SAS Institute, Cary NC).

Results

Maternal and Child Demographic Characteristics. The participants included in the present analysis consisted of mothers and their infant born between April 2014 and August 2015 from the Western Cape Province of South Africa who participated in a follow-up study to examine social-emotional development and cognitive development at approximately three years of age. A total of n=18 mother-infant dyads were excluded due to missing maternal prenatal mental health data. The final sample consisted of 600 maternal-infant dyads (274 females; gestational age at birth: 38.89 weeks \pm 2.03) (Table 1).

Child Social-Emotional Development. Based on the BITSEA problem scale percentile rank score of 26 or higher, 51% of children (306/600) were classified as having a “possible problem”. Based on the BITSEA competence scale percentile rank score of 15 or lower, 5% (30/600) of children were classified in the “possible deficit/delay range” for social competencies (Table 2). There were no significant sex differences in social-emotional problems on the BITSEA, however girls had significantly higher social-emotional competence compared to boys (mean difference: 0.38, CI: 0.05, 0.71, $p = 0.03$)

Association between Prenatal Maternal Depression, Trait Anxiety, and Child Social-Emotional Development. Compared to children born to mothers with no prenatal depression or trait anxiety, children born to mothers with prenatal depression and trait anxiety had higher social-emotional problems (mean difference: 4.66; 95% CI 3.43, 5.90), followed by prenatal maternal trait anxiety only (mean difference: 3.87; 95% CI 2.07, 5.66), and finally prenatal maternal depression only (mean difference: 2.76; 95% CI 1.23, 4.29) in minimally adjusted

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3 models. These associations remained significant in fully adjusted models where similarly
4 comorbid prenatal maternal depression and trait anxiety group was associated with the highest
5 child social-emotional problems (mean difference: 4.33; 95% CI 2.90, 5.67), followed by
6 prenatal maternal trait anxiety only (mean difference: 3.23; 95% CI 1.19, 5.27), with the smallest
7 mean difference for prenatal maternal depression only group (mean difference: 2.64; 95% CI
8 1.02, 4.27) as compared to the no prenatal depression or trait anxiety group (Figure 1).

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16 Additional significant predictors in the multivariate models were parity of 3 or greater which was
17 associated with lower social-emotional problems (mean difference: -3.02, 95% CI -4.63, -1.40)
18 and low continuous smoking during pregnancy which was associated with higher social-
19 emotional problems (mean difference: 1.39, 95% CI 0.039, 2.74). There were no significant
20 associations between prenatal maternal depression, trait anxiety, and child social-emotional
21 competence.
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31 *Association between Prenatal Maternal Depression, State Anxiety, and Child Social-*
32 *Emotional Development.* Compared to children born to mothers with no prenatal depression or
33 state anxiety, children born to mothers with comorbid prenatal depression and state anxiety had
34 higher social-emotional problems (mean difference: 4.29; 95% CI 2.73, 5.84). Children born to
35 mothers with prenatal depression only also had higher social-emotional problems compared to
36 mothers with no prenatal depression or state anxiety (mean difference: 2.71; 95% CI 1.51, 3.88).
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3 associated with higher social-emotional problems (mean difference: 1.44; 95% CI 0.075, 2.81),
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5 and finally less than a high school education (some primary school only) which was associated
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7 with higher social-emotional problems (mean difference: 3.47; 95% CI 0.248, 6.70). However,
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9 there was no significant association between prenatal state anxiety only and child social-
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11 emotional problems on the BITSEA. There were also no significant associations between
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13 prenatal maternal depression, state anxiety, and social-emotional competence.
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17 *Child Cognitive, Language, and Motor Development.* Based on normative cognitive
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19 cutoff scores defined by the BSID-III ST, 4% of children (24/600) were classified as at-risk
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21 (Table 2). Risk classification percentages were similar across all subdomains, expressive
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23 language: 4% , receptive language: 6%, gross motor: 4%, and fine motor: 3%. There were no
24
25 significant sex differences in child cognitive scores.
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29 *Association between Prenatal Maternal Depression, Trait Anxiety, and Child Cognitive,*
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31 *Language, and Motor Development.* Compared to children born to mothers with no prenatal
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33 depression or trait anxiety, children born to mothers with comorbid prenatal depression and trait
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35 anxiety had lower cognitive scores on the BSID-III ST (mean difference: -1.04; 95% CI -1.99, -
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37 0.08). Results remained significant in the fully adjusted model (mean difference: -1.11; 95% CI -
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39 2.13, -0.09) (Figure 2) and in posthoc analyses where we additionally controlled for language of
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41 administration for the BSID-III ST (mean difference: -0.51, 95% CI -0.99, -0.042). Children who
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43 were assessed on the BSID-III ST in Afrikaans (mean difference: -1.00, 95% CI -1.48, -0.52) or
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45 who were assessed in mixed English and Afrikaans (mean difference: -1.30, 95% CI -2.07, -
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47 0.54) has significantly lower cognitive scores compared to children assessed in English. Low
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49 continuous prenatal maternal alcohol use was also associated with lower cognitive scores (mean
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51 difference: -1.30; 95% CI -2.36, -0.24).
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3 *Association between Prenatal Maternal Depression, State Anxiety, and Child Cognitive,*
4 *Language, and Motor Development.* Compared to children born to mothers with neither prenatal
5 depression nor trait anxiety, there was no significant association between cognitive scores for
6 children born to mothers with prenatal depression only, prenatal trait anxiety only, or combined
7 prenatal depression and trait anxiety in either the minimally or fully adjusted models.
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17 **Discussion**

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19 In summary, we found the greatest increase in child social-emotional problems in
20 children born to women with comorbid prenatal depression and trait anxiety compared to women
21 with no prenatal depression or trait anxiety, prenatal depression alone, or prenatal trait anxiety
22 alone. We additionally found a significant association between comorbid prenatal maternal
23 depression and state anxiety on higher child social-emotional problems; however, we found no
24 association between prenatal maternal state anxiety in the absence of prenatal maternal
25 depression on child social-emotional problems. Finally, we reported children born to mothers
26 with prenatal maternal depression and trait anxiety had lower cognitive scores on the BSID-III
27 ST, but we did not find an association between prenatal maternal depression alone on cognitive
28 outcomes at 3-years of age.
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42 Our finding linking prenatal maternal depression and anxiety to social-emotional risk
43 parallels two recent South African studies linking increased prenatal maternal stressors to higher
44 behavioral problems in children with an odds ratio of 2.52, but not before 4 years of age²⁹ and
45 increased perinatal depression to aggressive behaviors at 60 months of age²⁴. Our findings are
46 also largely consistent with a recent meta-analysis of studies predominately conducted in HICs,
47 which found prenatal maternal depression and anxiety were associated with higher social-
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3 emotional problems in offspring with larger effect sizes for prenatal maternal depression (OR
4 1.79; 95% CI 1.61 - 1.99) compared to prenatal maternal anxiety (OR 1.50, 95% CI, 1.36 -
5 1.64)⁶. We found the greatest increase in child social-emotional problems in children born to
6 women with comorbid prenatal depression and trait anxiety and no effect of prenatal maternal
7 state anxiety in the absence of prenatal maternal depression on child social-emotional problems.
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9 Our results are suggestive that chronic anxiety measured via trait anxiety may be more predictive
10 of child social-emotional outcomes than a single measurement of concurrent anxiety during
11 pregnancy.
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21 A prior meta-analysis⁶ also found stronger effects of prenatal maternal depression and
22 anxiety on child social-emotional outcomes when sociodemographic risk factors such as low-
23 income, lower levels of parental education, or single family households, were highest⁶. Similarly,
24 we found that lower levels of maternal education, low continuous tobacco use during pregnancy,
25 and low continuous alcohol use during pregnancy were associated with higher social-emotional
26 problems in children at three years of age. Intriguingly, maternal parity of 3 or greater was
27 protective and associated with lower social-emotional problems which may be due to reduced
28 depression and anxiety levels in women with higher parity, changes in the perception of their
29 child's behavior due to having multiple children, or additional social opportunities during sibling
30 interactions^{44 45}.
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44 The Drakenstein Child Health Study based in the Western Cape found approximately
45 50% of the overall sample (369/731) were categorized as having cognitive delay at two years of
46 age based on cutoffs defined by United States (US) normative data³⁰. Better cognitive outcomes
47 were associated with higher maternal education, older child age, a primigravid mother, and
48 higher socioeconomic status whereas prenatal maternal depression was associated with a 1.03
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3 SD (95% CI -1.94 to -0.12) reduction in cognitive scores on the Bayley Scales of Infant and
4 Toddler Development at two years of age³⁰. Similar to the Drakenstein Child Health Study³⁰, we
5 found children born to mothers with prenatal maternal depression and trait anxiety had lower
6 cognitive scores on the BSID-III ST compared to the no prenatal maternal depression or trait
7 anxiety group. In contrast, we did not find an association between prenatal maternal depression
8 alone on cognitive outcomes at 3-years of age. However, since we did not utilize the full BSID-
9 III and only administered the BSID-III ST, it is difficult to directly compare our results to The
10 Drakenstein Child Health study findings. Moreover, both studies relied on US normative data to
11 define cutoff scores.
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24 More recently, a large home-visiting intervention study based in Cape Town examined
25 the effect of prenatal maternal depression only, postnatal maternal depression only (birth – 60
26 months), or recurrent pre- and postnatal maternal depression. This study also accounted for
27 several other risk factors including intimate partner violence, HIV status, and alcohol use on
28 child social behaviors, language skills, and cognitive development. No associations were found
29 between maternal depression at any time point with children's language or cognitive
30 development at 36 or 60 months of age²⁴. However, children of never depressed mothers had
31 lower aggressive behaviors on the Child Behavior Checklist at 60 months of age than children of
32 mothers with postnatal depression only or perinatal depression²⁴.
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44 There are several biological mechanisms which can explain prior studies and our current
45 findings linking prenatal maternal depression and anxiety with child social-emotional behaviors
46 and cognitive development such as increased prenatal maternal inflammation, increased cortisol
47 production, and/or epigenetic changes⁴⁶⁻⁵⁵. Pregnancy is associated with changes in inflammatory
48 processes and increased placental cortisol production with reduced maternal HPA axis sensitivity
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3 to stress^{46 47}. However, prenatal maternal depression may upregulate inflammatory processes
4 and/or cortisol production. Additionally, prior research found women with comorbid depression
5 and anxiety have the greatest increases in salivary cortisol levels¹⁸. Maternal cortisol can cross
6 the placenta resulting in increased inflammation^{46 47} and/or affect the developmental of limbic
7 regions, which are associated with social and emotional processes⁵⁶. In animal models, increased
8 proinflammatory proteins have been associated with widespread changes in perinatal brain
9 development such as with volume reductions in gray and white matter, decreased density of
10 GABAergic neurons, reduced synaptic pruning, and network dysfunction with potential
11 downstream effects on neurobehavioral development⁴⁸⁻⁵⁵. Other studies examining the
12 intergenerational transmission of trauma have demonstrated transgenerational epigenetic changes
13 in animal models⁵⁷. It is also possible comorbid maternal depression and trait anxiety may
14 indicate a specific phenotype that is genetically transmitted to the next generation resulting in
15 psychosocial sequelae in offspring. Taken together, prior research suggests multiple overlapping
16 pathways by which prenatal maternal mood can affect offspring brain-behavioral development.

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19 While we report an association of prenatal maternal depression and anxiety with child
20 social-emotional and cognitive development from a prospective cohort study with a fairly large
21 sample of participants, there are several methodological and contextual limitations within the
22 current study that are worth noting. First, it is important to note that the reliance on maternal-
23 report measures to characterize child social-emotional development is a limitation in the majority
24 of research to date, including the present study. The reliance on maternal reporting of child
25 social-emotional development may be influenced by factors such as maternal mood or education.
26 An additional limitation was the use of the BSID-III screening test in the current study to
27 measure cognitive development, which is based on US normative data. Future studies should

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3 consider objective measures of child social-emotional development through observational or
4 behavioral coding paradigms in addition to utilizing objective cognitive developmental
5 assessments of with normative data in South African children.
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10 There are also several unmeasured contextual factors which could affect our findings. For
11 example, although prenatal maternal and child nutrition are known to affect child
12 neurobehavioral development, we lacked measures of prenatal maternal nutrition, prenatal
13 maternal micronutrient deficiencies, prenatal and postnatal household food insecurity, and
14 information regarding child nutrition. Additionally, prior studies have emphasized the
15 importance of measuring childhood trauma, maternal stress, and social support within
16 communities with several heterogeneous risk factors³, these measures were not collected as part
17 of the original NIH Safe Passage Study or our recent follow-up study. Therefore, we could not
18 examine their effects or consider maternal social support as a potential moderator of resilient
19 neurodevelopmental outcomes. There is also robust literature examining both postpartum
20 depression (PPD) and the early mother-infant relation in shaping child outcomes. Two prior
21 studies in South Africa demonstrated maternal intrusiveness and coerciveness mediated the
22 association between maternal PPD and early childhood attachment^{58 59}. In the current study, we
23 did not collect data postnatally between birth and three years of age. Additionally, we did not
24 collect postnatal information on maternal depression, anxiety, or stress. Therefore, due to this
25 methodological limitation we cannot draw conclusions regarding the combined effect of the pre-
26 and postnatal environment on child neurodevelopmental outcomes, nor can we assess potential
27 interaction effects between pre- and postnatal maternal mood on child social-emotional and
28 cognitive outcomes. Finally, our results may not generalize to all South African populations
29 where HIV rates can be as high as 35% since our cohort only included one woman with HIV.
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3 Strengths of the current analyses include our large sample size, evaluation of both cognitive and
4 social-emotional outcomes within the same cohort, finally the detailed prospective collection of
5 both depression and anxiety symptoms during pregnancy³¹ in addition to other potential
6 confounders.
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12 Our results suggest comorbid prenatal maternal depression and chronic anxiety have a
13 greater impact on child social-emotional and cognitive development than either condition alone
14 or than comorbid prenatal maternal depression and transitory anxiety during pregnancy. These
15 findings are supported by a robust literature within the DOHaD framework linking perturbations
16 in the gestational environment to later neurodevelopmental or psychiatric sequelae. Our results
17 also lend support for future intervention studies aimed at perinatal mental health interventions
18 targeting maternal depressive and anxiety symptoms to improve long-term child social-emotional
19 and cognitive developmental outcomes in low-resource communities.
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Table 1 - Sociodemographic characteristics		
	Mean ± SD or N (%)	N and Percent Missing (%)
Maternal Characteristics		
Maternal Age (years)	25.26 ± 5.91	0 (0%)
Maternal Body Mass Index (BMI)		0 (0%)
BMI <18.5 (kg/m ²)	62 (10.33%)	
BMI 18.5-25 (kg/m ²)	282 (47%)	
BMI 25-30 (kg/m ²)	132 (22%)	
BMI >30 (kg/m ²)	124 (20.67%)	
Parity		0 (0%)
Parity <1	218 (36.33%)	
Parity =1	196 (32.67%)	
Parity =2	103 (17.17%)	
Parity ≥3	83 (13.83%)	
Antenatal care visits		0 (0%)
antenatal care visit <3	49 (8.17%)	
antenatal care visit 3-6	389 (64.83%)	
antenatal care visit >6	162 (27%)	
Cesarean Section	106 (17.70%)	1 (0.1%)
Education		0 (0%)
Some primary school	43 (7.167%)	
Some high school	405 (67.57%)	
Completed high school	119 (19.83%)	
Beyond high school	33 (5.5%)	
Married	290 (48.33%)	0 (0%)
Employed	172 (28.67%)	0 (0%)
Adjusted Household Crowding	1.56 ± 0.72	2 (0.33%)
Depression (Edinburgh ≥13)	333 (55%)	0 (0%)
Anxiety (State-Trait Anxiety Inventory ≥40)	115 (19.17%)	0 (0%)
Maternal Prenatal Alcohol Use Cluster Groups		0 (0%)
Non drinking group: 0 standard drinks/trimester	245 (46.93%)	
Moderate-high continuous drinking group:	122 (23.37%)	
Standard drinks in Trimester 1	27 ± 39	
Standard drinks in Trimester 2	17 ± 25	

	Standard drinks in Trimester 3	9.4 ± 15	
	Binge drinking events (≥ 4 drinks/day) Trimester 1	2.7 ± 4	
	Binge drinking events (≥ 4 drinks/day) Trimester 2	1.7 ± 2.8	
	Binge drinking events (≥ 4 drinks/day) Trimester 3	0.89 ± 1.7	
	Low continuous drinking	26 (4.98%)	
	Standard drinks in Trimester 1	1.4 ± 2.5	
	Standard drinks in Trimester 2	4 ± 2.8	
	Standard drinks in Trimester 3	0.62 ± 1.1	
	Binge drinking events (≥ 4 drinks/day) Trimester 1	0.067 ± 0.25	
	Binge drinking events (≥ 4 drinks/day) Trimester 2	0.30 ± 0.46	
	Binge drinking events (≥ 4 drinks/day) Trimester 3	0 ± 0	
	Quit early drinking	129 (24.71%)	
	Standard drinks in Trimester 1	8.5 ± 6.5	
	Standard drinks in Trimester 2	0.31 ± 0.87	
	Standard drinks in Trimester 3	0.056 ± 0.31	
	Binge drinking events (≥ 4 drinks/day) Trimester 1	0.84 ± 0.82	
	Binge drinking events (≥ 4 drinks/day) Trimester 2	0 ± 0	
	Binge drinking events (≥ 4 drinks/day) Trimester 3	0 ± 0	
	Maternal Prenatal Tobacco Use		2 (0.33%)
	Non smoking (0 cigarettes/trimester)	227 (37.97%)	
	Moderate-high continuous smoking	132 (22.07%)	
	Average Cigarettes in Trimester 1	45 ± 20	
	Average Cigarettes in Trimester 2	50 ± 27	
	Average Cigarettes in Trimester 3	48 ± 25	
	Low continuous smoking	222 (37.12%)	
	Average Cigarettes in Trimester 1	16 ± 9.4	
	Average Cigarettes in Trimester 2	16 ± 9.7	
	Average Cigarettes in Trimester 3	16 ± 10	
	Quit early smoking	17 (2.84%)	
	Average Cigarettes in Trimester 1	11 ± 7.5	
	Average Cigarettes in Trimester 2	0.15 ± 0.32	
	Average Cigarettes in Trimester 3	0.079 ± 0.11	
	Raw Maternal Edinburgh Score	12.99 ± 5.73	0 (0%)
	Raw Maternal State Anxiety Score	31.23 ± 10.24	0 (0%)
	Raw Maternal Trait Anxiety Score	40.63 ± 10.63	0 (0%)
	Depression - Trait Anxiety Groups		0 (0%)
	No depression or trait anxiety	199 (33.17%)	
	Depression alone	106 (17.67%)	
	Trait anxiety alone	68 (11.33%)	
	Depression and trait anxiety	227 (37.83%)	

Depression - State Anxiety Groups			0 (0%)
	No depression or state anxiety	248 (41.33%)	
	Depression alone	237 (39.50%)	
	State anxiety alone	19 (3.17%)	
	Depression and state anxiety	96 (16%)	
HIV status			
	Tested for HIV	600 (100%)	
	HIV positive	1 (0.1%)	
Infant Characteristics			
Infant Sex			0 (0%)
	Male	326 (54.33%)	
	Female	274 (45.67%)	
Gestational age at birth (weeks)		38.89 ± 2.03	0 (0%)
Infant Birth weight (grams)		2980.65 ± 564.65	2 (0.33%)
Follow-up age (months)		38.29 ± 2.96	0 (0%)
Adjusted follow-up age (months)		38.14 ± 0.016	0 (0%)

Table 2. Neurodevelopmental Outcome Raw Scores and At-risk Groups

BSID-III Screening Test Language of Administration			
	English Only	177 (30%)	
	Afrikaans Only	360 (62%)	
	Mixed English and Afrikaans	48 (8%)	
BSID-III Screening Test Scores			
	Gross motor	25.47 ± 4.54	
	Fine motor	23.55 ± 4.08	
	Cognitive	27.77 ± 4.99	
	Problem solving	13.40 ± 6.77	
	Receptive language	21.69 ± 5.10	
	Expressive language	21.27 ± 3.78	
At-Risk Categories			
	Gross motor	21 (4%)	
	Fine motor	18 (3%)	
	Cognitive	24 (4%)	
	Receptive language	33 (6%)	
	Expressive language	25 (4%)	
Brief Infant Toddler Social-Emotional Assessment (BITSEA)			
	Social Emotional Problem	13.40 ± 6.77	
	Competence	19.56 ± 2.07	

At-Risk Categories	
Social Emotional Problems	306 (51%)
Social-Emotional Competence	30 (5%)

Figure Legends

Figure 1. Association between prenatal maternal depression, prenatal maternal anxiety, and child social-emotional problems measured by the BITSEA. Each line plot depicts the mean difference and their confidence interval for child social-emotional problems (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

Figure 2. Association between prenatal maternal depression, prenatal maternal anxiety, and child cognitive development measured by the BSID-III Screening Test. Each line plot depicts the mean difference and their confidence interval for child cognitive development (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

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3 **Contributors:** WPF and HJO acquired funding for and designed the work. LCS, AS, NHB, ML,
4 YR, PES, HJO, and WPF conceptualized the work. MP, PES, CDP, and HJO acquired the data.
5
6 LCS, NHB, and WPF led in data collection oversight and quality control. AS, LCS, and YR
7
8 analyzed the data. All authors contributed to the interpretation of data and drafting the work and
9
10 revising it critically for important intellectual content. All authors approved the final manuscript
11
12 and agree to be accountable for all aspects of the work.
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19 **Acknowledgements:** We would like to acknowledge Lucy Brink, J. David Nugent, and Daianna
20
21 Rodriguez for their database and administrative support. We would also like to thank all of the
22
23 families who participated in this research study for making this work possible.
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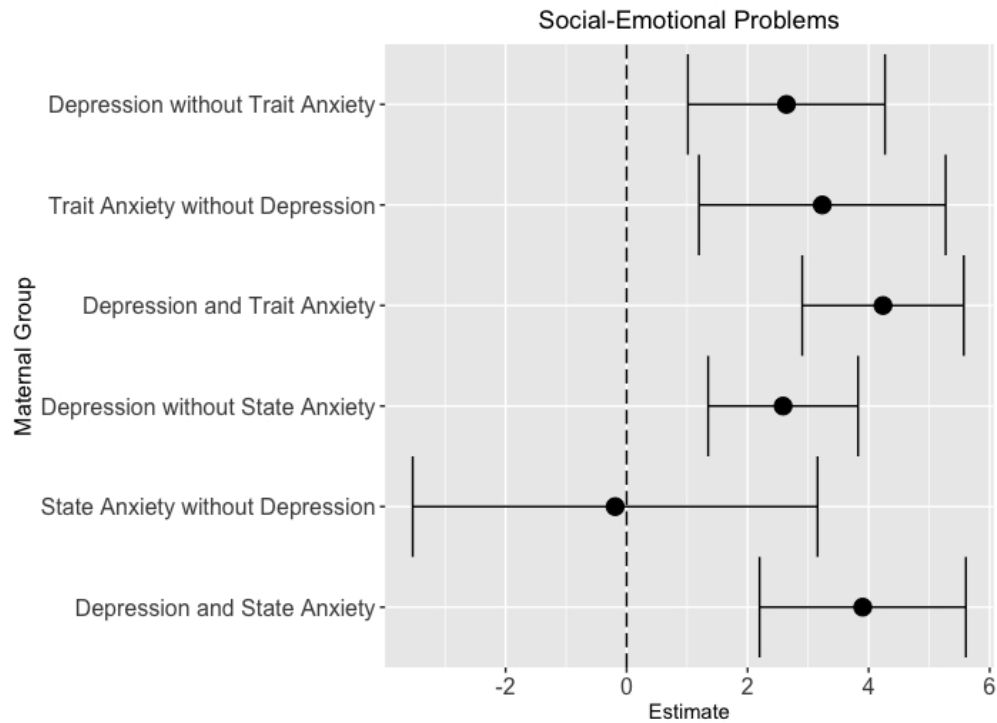
28 **Ethics statements**

29 **Patient consent for publication**

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31 Not applicable.
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38 **Ethics approval**

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40 Ethics approval was received from the Institutional Review Boards and ethics review committees
41
42 at Stellenbosch University (N16-08-101 and N06-10-210) and the New York State Psychiatric
43
44 Institute (5338). All participants provided informed written consent at both time points (prenatal
45
46 and postnatal) before inclusion in the study.
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Figure 1. Association between prenatal maternal depression, prenatal maternal anxiety, and child social-emotional problems measured by the BITSEA. Each line plot depicts the mean difference and their confidence interval for child social-emotional problems (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

247x181mm (72 x 72 DPI)

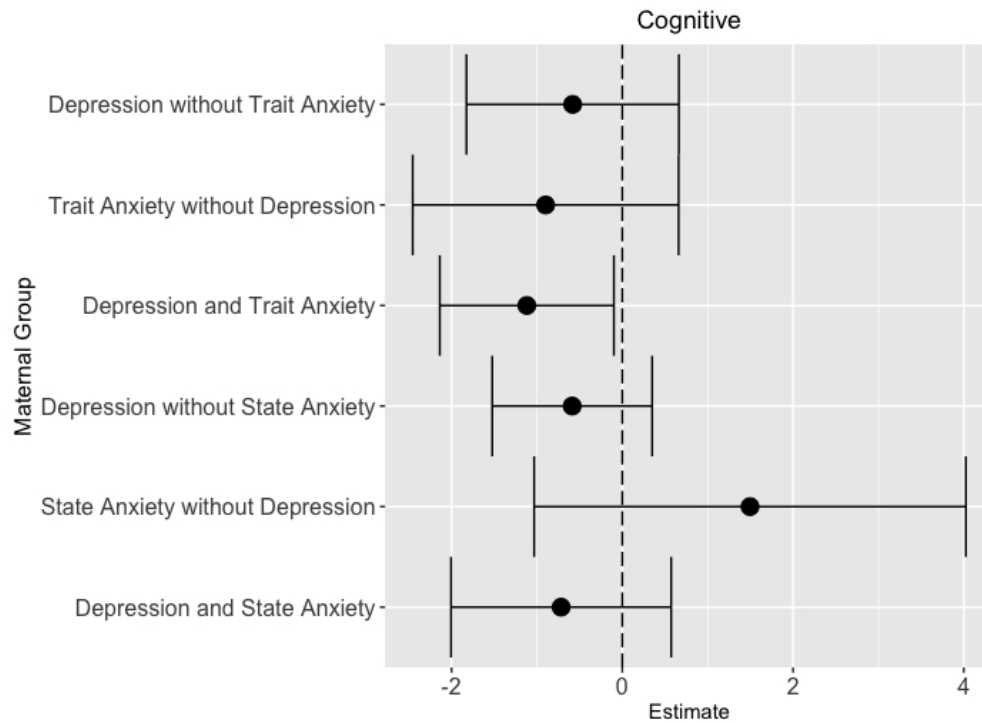


Figure 2. . Association between prenatal maternal depression, prenatal maternal anxiety, and child cognitive development measured by the BSID-III Screening Test. Each line plot depicts the mean difference and their confidence interval for child cognitive development (x-axis) for each prenatal maternal mental health group (y-axis). Either no prenatal maternal depression and state anxiety or no prenatal maternal depression and trait anxiety were the reference groups. Models were adjusted for sex, gestational age at birth, age at follow-up, prenatal maternal alcohol use, prenatal maternal tobacco use, maternal employment status at delivery, maternal educational attainment at delivery, parity, and the household crowding index.

247x181mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	2 3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7 - 9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 - 9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7 - 9 N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9 - 10
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 - 10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9 - 10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	9 - 10 9 - 10 10 10 N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11 11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9, 11 - 13 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11 - 13
2			(b) Report category boundaries when continuous variables were categorized	N/A
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4				
5				
6				
7				
8				
9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11 - 13
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	14
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	17
20				
21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1
23				
24				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.