Journal of Developmental Origins of Health and Disease

cambridge.org/doh

Original Article

Cite this article: Milgrom J, Holt CJ, Bleker LS, Holt C, Ross J, Ericksen J, Glover V, O'Donnell KJ, de Rooij SR, Gemmill AW. (2019) Maternal antenatal mood and child development: an exploratory study of treatment effects on child outcomes up to 5 years. *Journal of Developmental Origins of Health and Disease* **10**: 221–231. doi: 10.1017/S2040174418000739

Received: 27 March 2018
Revised: 15 August 2018
Accepted: 4 September 2018
First published online: 10 October 2018

Key words:
antenatal anxiety; antenatal depression; child neurodevelopment; cognitive-behavioural therapy; intervention

Address for correspondence:
L. S. Bleker, Department of Clinical Epidemiology, Bioinformatics and Biostatistics, Amsterdam UMC, location AMC, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. E-mail: l.s.bleker@amc.uva.n

CAMBRIDGE UNIVERSITY PRESS

Maternal antenatal mood and child development: an exploratory study of treatment effects on child outcomes up to 5 years

J. Milgrom[1,2], C. J. Holt[1], L. S. Bleker[3], C. Holt[1], J. Ross[1], J. Ericksen[1], V. Glover[4], K. J. O'Donnell[5,6], S. R. de Rooij[3] and A. W. Gemmill[1]

[1]Parent-Infant Research Institute, Heidelberg West, Victoria, Australia, [2]Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia, [3]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, location AMC, Amsterdam, The Netherlands, [4]Institute of Reproductive and Developmental Biology, Imperial College London, London, UK, [5]Douglas Hospital Research Centre, McGill University, Montreal, Canada and [6]Canadian Institute for Advanced Research, Child and Brain Development Program, Toronto, Canada

Abstract

Effective treatment of maternal antenatal depression may ameliorate adverse neurodevelopmental outcomes in offspring. We performed two follow-up rounds of children at age 2 and age 5 whose mothers had received either specialized cognitive-behavioural therapy or routine care for depression while pregnant. Of the original cohort of 54 women, renewed consent was given by 28 women for 2-year follow-up and by 24 women for 5-year follow-up. Child assessments at the 2-year follow-up included the Parenting Stress Index (PSI), Bayley Scales of Infant Development (BSID-III) and the Child Behaviour Checklist (CBCL). The 5-year follow-up included the Wechsler Preschool and Primary Scales of Intelligence (WPPSI-III) and again the CBCL. Treatment during pregnancy showed significant benefits for children's development at age 2, but not at age 5. At 2 years, intervention effects were found with lower scores on the PSI Total score, Parent Domain and Child domain ($d = 1.44$, 1.47, 0.96 respectively). A non-significant trend favoured the intervention group on most subscales of the CBCL and the BSID-III (most notably motor development: $d = 0.52$). In contrast, at 5-year follow-up, no intervention effects were found. Also, irrespective of treatment allocation, higher depression or anxiety during pregnancy was associated with higher CBCL and lower WPPSI-III scores at 5 years. This is one of the first controlled studies to evaluate the long-term effect of antenatal depression treatment on infant neurodevelopmental outcomes, showing some benefit. Nevertheless, caution should be taken interpreting the results because of a small sample size, and larger studies are warranted.

Introduction

Although substantial evidence points to the detrimental impact of depression and anxiety in pregnancy on infant neurodevelopmental outcomes, there currently exists almost no published research evaluating whether this can be ameliorated by antenatal treatment of maternal mood[1]. During pregnancy, the estimated prevalence rates of depression are 7.4%, 12.8% and 12.0% for the first, second, and third trimester, respectively.[2,3] The overall estimated prevalence for a clinical diagnosis of any anxiety disorder in pregnancy is 15.2%.[4] Depression and anxiety have profound repercussions for maternal well-being and incur large economic costs. A recent analysis by the London School of Economics has demonstrated that perinatal mental health problems together cost £8 billion for every 1-year cohort of births in the UK, the majority of which are attributable to the enduring negative impact on children's developmental prospects.[5]

There is substantial evidence on the impact of antenatal maternal distress on neurodevelopmental outcomes in infants and a growing understanding of the underlying mechanisms that may be involved. Many experimental studies in rodents and non-human primates report that offspring of mothers exposed to chronic antenatal stress show heightened responses to stress, and cognitive impairments.[6–8] At the same time, a growing clinical literature links antenatal maternal depression and anxiety with negative effects on the developing fetus and poor long-term child neurodevelopmental outcome. Maternal prenatal anxiety or depression predicted altered fetal behaviour (heart rate and motor activity) and reduced scores on early neonatal assessments of temperament.[9] Attention deficit hyperactivity disorder,[10,11] emotional

problems[12–14] and impaired cognitive development[12,15,16] are consistently reported longer-term problems for children of antenatally depressed or anxious mothers. O'Donnell *et al.* reported an approximately two-fold increase in prevalence rates of emotional/behavioural disorders in children and adolescents exposed to high levels of maternal prenatal anxiety or depression.[13]

The mechanisms through which maternal antenatal depression and anxiety may affect fetal development *in utero* are likely to involve a number of biological systems including, but not limited to, altered brain structure, estrogen, serotonin and neurotrophin signalling pathways, the HPA axis and (placental) glucocorticoid regulation.[13,17–19] For example, increased placental transfer of cortisol may occur via downregulation of the enzyme that deactivates cortisol, 11β–hydroxysteroid dehydrogenase type II (*11β–HSD2*),[20,21] with neurotoxic effects leading to behavioural and emotional changes in later life, as has been shown in human primates.[22,23] Also, maternal depression and anxiety may cause epigenetic modifications in fetal genes involved in neurodevelopment, for example by DNA methylation or histone modification, leading to changes in gene expression and function.[24] In observational human studies, antenatal maternal mood has been associated with structural variation in the hippocampus, amygdala and prefrontal regions in neonates,[25,26] and also with alterations in DNA methylation status involved in stress reactivity, such as the glucocorticoid receptor (*NR3C1*).[24,27]

Although substantial evidence from longitudinal studies points to the detrimental impact of depression and anxiety in pregnancy on offspring neurodevelopment, only an interventional randomized controlled trial (RCT) can test whether adverse infant neurodevelopmental outcomes can be ameliorated by antenatal treatment of maternal mood. Currently, there are two relevant published trials – our small pilot RCT validating the efficacy of our antenatal cognitive-behavioural therapy (CBT) treatment for depression and anxiety, which reported improved infant outcomes to 9 months of age,[28] and a small treatment study reporting on early neonatal temperament and sleep patterns by Netsi and colleagues.[9] In the latter trial, infant sleep duration and temperament 2 months postpartum was measured in offspring from women who had been treated for antenatal depression either with CBT or treatment as usual (TAU) for antenatal depression. Although they could not detect an evident treatment effect, they showed that improvement in depression scores during pregnancy was associated with easier temperament and short nocturnal sleep duration.

In our pilot RCT[28] women and their infants ($n = 54$) were assessed when infants were 9 months of age. Large treatment effects on maternal depression and anxiety favouring the intervention were sustained at 9 months.[28] Large, significant treatment effects were also observed in infant problem solving, self-regulation and stress reactivity. Here we report a follow-up from this pilot RCT cohort of offspring at 2 years and 5 years. Both follow ups included blinded, observer-rated measures of neurodevelopment as well as mother-reported measures of child behaviour. In the context of the RCT of depression intervention we specifically hypothesised that: children whose mothers received specialised CBT for antenatal depression and anxiety would exhibit more favourable scores on developmental outcomes at the 2-year and 5-year follow-ups compared to children whose mothers received TAU. In addition, as previous evidence suggests that the severity of depression or anxiety in pregnancy correlates with neurodevelopmental outcomes in the offspring, we planned to additionally explore this association in our sample. We examined whether any underlying relationship exists, specifically whether severity of baseline anxiety and depression scores in pregnancy would show an inverse relationship with favourable child outcomes, despite treatment.

Methods

Design

This study was a longitudinal follow-up of a cohort from a previously reported[28] parallel two-group RCT comparing CBT treatment for antenatal depression and anxiety to TAU. At baseline, 54 pregnant women enrolled in the RCT, all of whom gave consent, were aged ≥18 years, less than 30 weeks pregnant and met diagnostic criteria for major or minor depression or adjustment disorder with mixed depression and anxiety using the Structured Clinical Interview for the DSM-IV (SCID).[29] As measured by the Beck Depression Inventory (BDI),[30] the severity of pregnant women's depression symptoms in the full sample at baseline was, on average, in the severe range with a mean of 30.7 (SD = 9.4).[28] Half were allocated to either the Beating the Blues before Birth treatment program, an 8-week CBT program, and half to TAU. TAU meant that women were either referred to their GP for further evaluation and management or that they would be case managed by their midwife, as would usually have happened in routine practice. Two consecutive follow-up studies involved re-consenting the families from the RCT at two-time points; when children had reached approximately 2 and 5 years of age. The Human Research Ethics Committees of Northern Health, Austin Health, and Mercy Health, Melbourne, Australia approved the RCT (Trial Registration ACTRN12607000397415) and both follow-up studies.

Recruitment of participants

Families who had participated in the pilot RCT were re-contacted by telephone and by e-mail and were asked to provide renewed consent to take part in the follow-up studies.

Maternal characteristics

Sociodemographic variables at baseline, 2 years and 5 years

Baseline information on place of birth, as well as gestational age, parity, annual family income and relationship status were collected from study files from the original RCT. Sociodemographic information, including current annual family income and relationship status was again collected through questionnaires which were completed by mothers, at 2- and 5-year follow-ups. Baseline characteristics were reasonably well balanced between the CBT and TAU group, except for parity, with seemingly fewer nulliparous women in the CBT group at baseline. A Mann–Whitney U test was performed and showed that this difference was not statistically significant ($U = 290$, $P = 0.13$ in the 2-year follow-up sample and $U = 52.5$, $P = 0.63$ in the 5-year follow-up sample), and therefore the regression analyses were performed without the inclusion of parity as a potential confounder. Also, current income in the CBT group seemed to be higher at the 5-year follow-up. Results showed that income ($U = 50.5$, $P = 0.22$) was not significantly different between the groups, and therefore the regression analyses were performed without the inclusion of parity or income as a potential confounder.

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

Mental Health at baseline, 2 years and 5 years

The BDI-II[30] is a widely used, self-reported, well-validated, 21-item clinical measure of severity of depression. The BDI-II has been validated against gold-standard diagnostic criteria in perinatal populations.[31]

The Beck Anxiety Inventory (BAI)[32] is a self-reported 21-item measure of anxiety with well-established properties, including in perinatal populations.[31] The BDI-II and BAI were completed at 2 and at 5 years, and symptom scores at baseline were collected from study files from the original RCT.

Response to treatment

To assess the rate of responsiveness to treatment in the initial RCT for both subsamples of the women that participated in the 2- and 5-year follow-up, we performed two analyses. First, we calculated the difference in BDI-II and BAI score before and after treatment in the RCT, and performed a student's *t*-test to assess the difference in mean change in BDI-II and BAI score between the CBT and TAU group of the subsamples at 2- and 5-year follow-up. Second, we created a threshold to define 'substantial response to treatment', and divided the women in both subsamples into those who showed a substantial response to treatment *v.* those who had not. 'Substantial response to treatment' was defined as; a reduction in BDI-II symptom score after treatment of 50% of the symptom score before treatment, plus a BDI-II score of 18 points or less after treatment, which is the upper threshold for the 'mild' depression category.

2-Year follow-up

Child cognitive and motor development

Bayley Scales of Infant Development (BSID-III).[33] This was the primary measure of cognitive and motor development at 2 years. The BSID-III is the most widely-used measure of child development, and yields information in cognitive and motor domains. It is clinician-administered and rated. Higher scores on the BSID-III are more favourable and indicate better performance on cognitive, language and motor tasks.

Parenting stress

The Parenting Stress Index (PSI)[34] measures parent–child relationship functioning and attachment by parent report. Responses produce six 'Child' and seven 'Parent' subscales (including an attachment subscale), that reflect child and parent characteristics that may contribute to overall stress in parents. A score for each domain, and a Total score is then calculated. Higher scores on the PSI are less favourable and indicate higher overall parental experience of stress and increased risk for dysfunctional parenting and child behaviour problems.

Child behaviour

Child Behaviour Checklist (CBCL).[35] The Total Problems Score and the composite Difficulties in Emotional Regulation Scale of the CBCL were the primary measures of behavioural development. The CBCL is a widely used diagnostic screening assessment, completed by caregivers, which in this study, were the children's mothers. It includes a preschool version for children aged 1.5–5 years, and a school-age version for children aged 6–18 years. At 2 years of age, we calculated and reported on seven subscale scores of the CBCL (Emotional/Reactivity, Anxiety/Depression, Somatic Problems, Withdrawn Behaviour, Sleeping Problems, Attention Problems, and Aggressive Behaviour), as well as Internalizing and Externalizing Behavioural Problems and Total Problems scores. Higher scores on the CBCL are less favourable and indicate more problems.

5-Year follow-up

Child cognition

Wechsler Pre-School and Primary Scale of Intelligence (WPPSI-III).[36] The WPPSI-III is an individually administered clinical instrument for assessing the intelligence of young children 2 years + 6 months to 7 years + 3 months of age. The tests provide composite scores in the Verbal IQ (acquired knowledge, verbal reasoning and comprehension and attention to verbal stimuli) Performance IQ (fluid reasoning, spatial processing, attention to detail, and visual–motor integration), Processing Speed (visual-motor processing speed and accuracy) and a composite measure that represents general intellectual ability – Full Scale IQ. The WPPSI-III was administered by one of the researchers, who was trained and blinded to the mothers' allocation to treatment.

Child behaviour

CBCL.[35] The Total Problems Score and the composite Difficulties in Emotional Regulation Scale of the CBCL were again the primary measures of behavioural development. Although the target age of the participating children at the second follow-up was 5 years, some children were older. Therefore, we used either the pre-school or school-age versions of the CBCL in the 5-year follow-up. Similar questions are grouped into empirically based syndrome scale scores. At 5 years of age, we calculated and reported on four subscales of the CBCL corresponding to the subscales included at the 2-year follow-up (Anxiety/Depression, Somatic Problems, Attention problems and Aggressive Behaviour), as well as Internalizing and Externalizing Behavioural Problems and Total Problems scores.

Statistical analyses

For each outcome, *a priori* treatment comparisons were conducted by fitting general linear models controlling for baseline depression and anxiety as covariates to yield comparisons of the relative effectiveness of the two modes of management. In no cases did the inclusion of baseline covariates in the models substantially change either parameter estimates or significance levels. For ease of interpretation, results are therefore presented unadjusted for variation in baseline covariates. Linear regression was used to assess the effects of baseline prognostic variables on outcomes. Effect sizes (Cohen's *d* [37]) are presented with 95% Confidence Intervals. Analyses were executed in IBM SPSS Statistics 22. Next, we conducted a series of univariate regressions using baseline BDI-II and BAI scores in pregnancy to predict the effect of antenatal depression and anxiety symptoms on child outcomes, irrespective of treatment allocation in the original RCT.

Results

Maternal characteristics

Response to treatment

We have previously reported that women who received the intervention showed a significant improvement in depression and anxiety.[28] For the particular subsamples of women that participated in the 2- and at 5-year follow-ups, there was an overall

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

Table 1. The sub-samples of mothers who responded to the 2-year and 5-year follow ups

	2-Year subsample		5-Year subsample	
	Intervention	TAU	Intervention	TAU
	N = 15	*N* = 13	*N* = 12	*N* = 12
Gestational age at enrolment in weeks (SD)	18.5 (7.3)	19.8 (5.6)	18.1 (7.5)	19.5 (5.5)
Nulliparous (%)				
Baseline	6 (40)	9 (69.2)	4 (33.3)	7 (58.3)
Mean BDI-II score (depression) (SD)				
Baseline	31.3 (11.2)	26.8 (10.3)	30.4 (9.5)	29.3 (10.0)
Post-treatment	11.2 (8.7)	15.6 (9.6)	13.0 (10.0)	19.5 (9.2)
Follow-up	12.3 (8.6)	14.6 (8.0)	16.1 (13.3)	14.6 (10.7)
Mean BAI score (anxiety) (SD)				
Baseline	21.2 (9.4)	19.1 (6.0)	18.8 (8.7)	19.1 (6.9)
Post-treatment	9.9 (8.9)	14.5 (8.1)	11.6 (9.9)	16.7 (7.0)
Follow-up	8.6 (7.4)	7.4 (5.1)	11.3 (8.9)	10.3 (9.9)
Substantial response to treatment (%)[a]	12 (80)	5 (38.5)	7 (58.3)	3 (25)
Born in Australia (%)	11 (73.3)	10 (76.9)	10 (83.3)	9 (75)
Antidepressant use (%)				
Baseline	–	2 (15.4)	1 (8.3)	1 (8.3)
Follow-up	1 (6.7)	6 (46.2)	2 (16.7)	7 (58.3)
Annual family Income, $AU (%)				
Up to 80,000	7 (46.7)	8 (61.5)	2 (16.7)	6 (50.0)
> 80,000	5 (33.3)	5 (38.5)	10 (83.3)	5 (41.7)
No answer	3 (20)	0	0	1 (8.3)
Relationship status (%)				
Married	10 (66.7)	9 (69.2)	8 (66.7)	7 (58.3)
De facto	4 (26.7)	3 (23.1)	1 (8.3)	2 (16.7)
Single	1 (6.7)	1 (7.7)	3 (26)	3 (26)

TAU, treatment as usual; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.
[a]Defined as a decrease of 50% or more in depression symptom score (BDI-II) plus a post-treatment depression symptom score (BDI-II) of 18 or lower, indicating minimal to mild depression.

pattern of larger improvements in depression and anxiety scores after treatment for the CBT group compared to TAU but this did not reach statistical significance ($P > .05$ in all cases). Nevertheless, the categorical subscales indicating a 'substantial response to treatment' *v.* 'no substantial response to treatment' showed that in both subsamples, the number of women with 'substantial response to treatment' was approximately double in the CBT compared to the TAU group.

2-Year follow-up

Attrition and demographics

Of the 54 families from the original RCT, 28 families were recontacted, 10 families could not be contacted and 16 declined to take part. Of 28 families who re-consented, a further 3 failed to keep the clinic appointment for the BSID-III child assessment such that only maternal-report data on child development were collected. The mean age of the children was 2.49 years in the intervention group and (SD = 0.33) and 2.53 years in the TAU group (SD = 0.47). As shown in Table 1 the subsample had lower baseline depression scores in the TAU group compared to the intervention group (although this was not significant, $P = .34$). As a group, those 28 women who re-consented did not differ from the 26 non-respondents in the severity of their baseline depression symptoms at the time of their enrolment in the original RCT (mean baseline BDI-II scores of 29.2 *v.* 32.4 respectively, $P = .19$; mean baseline BAI scores of 20.5 *v.* 22.8 respectively, $P = .41$). It is also notable that the majority of respondents from the intervention group had received a diagnosis of major depressive disorder in pregnancy, whereas around half of

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

Table 2. Summary of between-group differences in cognitive and motor outcomes 2 years

	Intervention	TAU		
	M (*SD*)	*M* (*SD*)		
	N = 13	*N* = 12	*d*	95% CI
Cognitive (BSID-III)	118.9 (13.7)	116.5 (15.1)	0.26	−0.54 to 1.03
Language (BSID-III)	106.3 (10.8)	105.2 (15.9)	0.16	−0.63 to 0.94
Motor (BSID-III)	120.3 (12.7)	113.7 (14.0)	0.52	−0.30 to 1.29

TAU, treatment as usual; BSID-III, Bayley Scales of Infant Development: higher scores are more favourable. For the BSID-III only 25 sets of child data were collected (see text). Effect sizes (Cohen's *d*) are shown with corresponding 95% confidence intervals.

the respondents from the TAU group had an initial diagnosis of minor depressive disorder. Further, six women in the TAU group reported using medication for depression compared to one woman in the intervention group, at the time of the 2-year follow-up.

Child cognitive and motor development

The between-group differences seen on the BSID-III and observed effect sizes (Cohen's *d*) are shown in Table 2. Motor development showed a medium-to-large effect size favouring the intervention. Cognitive performance and language skills showed smaller effect sizes in the same direction. However, none of the results reached statistical significance. Cronbach's alpha for internal consistency on the composite scale Total Cognition was 0.70.

Parenting stress

The Total score of the PSI favoured the intervention to a degree that was statistically significant (Table 3), with all subscales showing, on average, lower scores in the intervention representing medium to large effect sizes. In particular, the 'adaptability' subscale of the PSI, which is a subscale of the 'PSI Child Domain', which measures how readily a child regulates his or her own state in response to an emotional upset or a change of routine, showed a large treatment effect. Of the 'PSI Parent Domain', the 'Role Restriction' subscale showed the largest effect, which assesses the parent's sense of limited freedom and constrained personal identity as a result of the parenting role. Cronbach's alpha for internal consistency on the composite scales: Child Domain, Parent Domain and Total Parenting Stress were 0.80, 0.89 and 0.84 respectively.

Child behaviour

Whilst mean scores on four out of seven subscales calculated from the CBCL were lower in the intervention group, as was the Total Problems score and the combined Internalizing Behaviour and Externalizing Behaviour scores, none of these differences were statistically significant. The largest effect sizes on the CBCL were seen in the Anxious/Depressed and Withdrawn Behaviour subscale (Table 3). Cronbach's alpha for internal consistency on the Total Problems composite scale was 0.81.

5-Year follow-up

Attrition and demographics

We were unable to re-contact 9 families, 18 declined to take part in the follow-up study and 3 children fell outside of the target age range. Of 24 families who re-consented, a further 5 were not able to visit the clinic for the WPPSI-III such that only maternal-report data on child development were collected (Fig. 1). The mean age of the children was 5.66 years in the intervention group (SD = 1.19), and 5.92 years in the TAU group (SD = 1.02). No significant differences between participants and non-respondents were seen in terms of depression symptoms at enrolment in the

Table 3. Summary of between-group differences in behavioural outcomes 2 years

	Intervention	TAU		
	M (*SD*)	*M* (*SD*)		
	N = 15	*N* = 13	*d*	95% CI
PSI Distractibility	23.7 (4.6)	24.9 (3.6)	0.30	0.00–1.03
PSI Adaptability	22.2 (5.5)	27.0 (5.4)	0.88	0.10–1.64*
PSI Demandingness	18.6 (4.5)	21.1 (4.9)	0.52	0.00–1.26
PSI Mood	8.9 (2.6)	10.7 (2.4)	0.71	0.00–1.45
PSI Acceptability	10.1 (3.1)	11.2 (2.8)	0.37	0.00–1.09
PSI Reinforces Parent	7.9 (1.8)	9.3 (2.6)	0.67	0.00–1.43
PSI Child Domain	89.71 (16.71)	103.10 (13.43)	0.96	0.16–1.75*
PSI Competence	26.3 (6.0)	33.5 (7.9)	1.04	0.27–1.83*
PSI Isolation	13.0 (4.2)	17.1 (6.5)	0.75	0.00–1.51
PSI Attachment	14.4 (2.6)	15.7 (3.6)	0.43	0.00–1.17
PSI Role Restriction	17.3 (3.3)	21.5 (5.8)	0.91	0.15–1.67*
PSI Spouse Parenting	16.9 (5.9)	20.4 (5.7)	0.60	0.00–1.55
PSI Depression	20.0 (5.7)	24.6 (5.9)	0.80	0.00–1.55*
PSI Health	15.6 (2.4)	17.2 (1.6)	0.76	0.00–1.65
PSI Parent Domain	123.6 (23.6)	158.2 (22.1)	1.47	0.47–2.47*
PSI Total Score	213.6 (37.5)	266.4 (35.5)	1.44	0.41–2.46*
CBCL Total Problems	25.4 (17.7)	28.0 (14.2)	0.16	0.00–0.87
CBCL Emotional/ Reactivity	1.5 (1.7)	2.0 (2.0)	0.29	0.00–1.00
CBCL Anxiety/Depression	1.0 (1.2)	1.9 (2.0)	0.57	0.00–1.30
CBCL Somatic Complaints	1.5 (1.5)	1.1 (1.2)	0.34	−0.41–1.09
CBCL Withdrawn	0.9 (1.1)	1.6 (1.4)	0.58	0.00–1.32
CBCL Sleeping Problems	2.6 (2.9)	2.4 (2.4)	0.05	−0.69–0.79
CBCL Attention Problems	2.2 (1.7)	2.3 (1.8)	0.06	0.00–0.41
CBCL Aggressive Behaviour	9.2 (6.6)	10.4 (4.9)	0.20	0.00–0.91
CBCL Internalizing Behaviour	4.9 (4.1)	6.6 (6.0)	0.09	0.00–1.07
CBCL Externalizing Behaviour	11.4 (7.8)	12.7 (5.5)	0.35	0.00–0.90

TAU, treatment as usual; CBCL, Child Behaviour Checklist: lower scores are more favourable. PSI, Parenting Stress Index: lower scores are more favourable. Effect sizes (Cohen's *d*) are shown with corresponding 95% confidence intervals.
*$P < 0.05$.

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

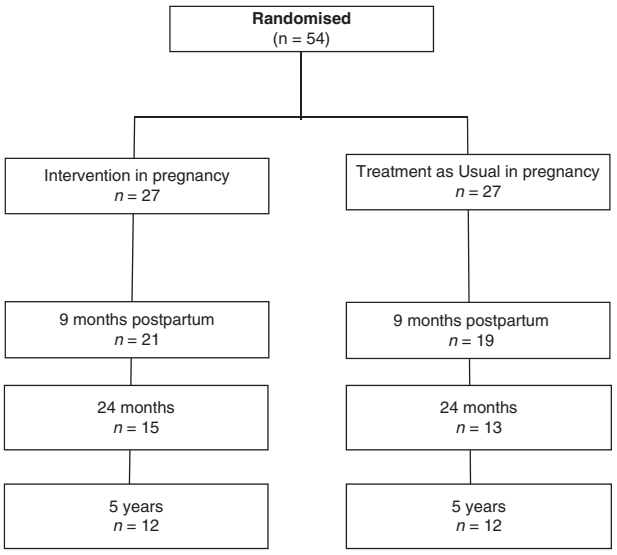

Fig. 1. Follow-up response rate for women in this study.

RCT (mean baseline BDI-II scores of 29.4 *v.* 31.6 respectively, $P = .40$; mean baseline BAI scores of 19.1 *v.* 23.6 respectively, $P = 0.12$). The subsample was also approximately balanced in terms of baseline BDI-II and BAI score between the intervention and treatment groups (Table 1). However, seven women in the TAU group reported using medication for depression compared to two women in the intervention group at the time of the 5-year follow-up.

Child cognition

Table 4 shows the between-group differences seen on the WPPSI-III and observed effect sizes (Cohen's *d*). No significant differences were found in Verbal, Performance, Processing or Full-Scale IQ scores between the intervention and the TAU groups. The largest effect size was seen on Performance IQ, in the opposite direction as was hypothesized, showing higher scores in the TAU group. Cronbach's alpha for internal consistency on the composite scale Full-Scale IQ score was 0.67.

Child behaviour

Table 5 shows behavioural subscale scores in the children of the intervention and the TAU groups. In 3 out of 5 subscales, the scores were equal or lower in the intervention group compared to the TAU group, as were Total Problems and Internalizing Behaviour. However, none of the differences was statistically significant. Cronbach's alpha for internal consistency on the composite scales: Internalizing Behaviour, Externalizing Behaviour and Total Problems Score were 0.87, 0.85 and 0.87 respectively.

Underlying relationship of antenatal mood and child outcomes

We aimed to explore whether previous findings in the literature indicating that symptom severity of depression and anxiety in pregnancy affect child outcomes, were also present in our sample. Although not significant, baseline anxiety scores accounted for the greatest proportion of the variance in models predicting the Language composite of the BSID-III and the Child Domain of the PSI at 2 years (Table 6). At 5 years, an association was found between higher baseline depression score and lower Verbal IQ, and with higher scores on the CBCL Anxiety/Depressed subscale, Social Behaviour, Rule-breaking Behaviour and Internalizing Behaviour. After adjusting for current depression, associations with the CBCL Anxiety/Depressed and Internalizing Behaviour survived. Higher symptoms of anxiety at baseline were associated with lower Verbal, Performance and Full-Scale IQ, and with higher scores on the CBCL Total Problems, Emotional/Reactivity, Anxiety/Depression, Withdrawn, Attention, Aggressive, Internalizing and Externalizing Behaviour. All associations survived adjusting for current anxiety symptoms, except the CBCL Attention Behavioural Problems scale (Table 7).

Table 4. Summary of between-group differences in cognitive outcomes 5 years

	Intervention	TAU		
	M (*SD*)	*M* (*SD*)		
	N = 11	*N* = 8	*d*	95% CI
Verbal – (WPPSI-III)	103.9 (10.5)	105.9 (13.8)	0.16	0.00–1.04
Performance – (WPPSI-III)	103.5 (12.9)	111.3 (17.7)	0.52	0.00–1.41
Processing Speed – (WPPSI-III)	103.7 (15.3)	101.3 (11.6)	0.17	−0.81–1.15
Full Scale – (WPPSI-III)	104.3 (11.2)	107.5 (14.7)	0.25	0.00–1.14

TAU, treatment as usual; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence: higher scores are more favourable. Effect sizes (Cohen's *d*) are shown with corresponding 95% confidence intervals.

Discussion

In the current study, we found some evidence to support our hypothesis that antenatal depression treatment improves child outcomes in the longer term. At 2-year follow-up, PSI scores were significantly lower in the intervention group and there was a trend toward more beneficial scores in the intervention group on most subscales of the CBCL and BSID-III, with some of the observed effect sizes of a magnitude that could be clinically important. However, at 5-year follow-up, these effects were no longer seen.

At 2 years, significant differences were found on the Total score and the Child and Parent Domain scores of the PSI and also on its associated subscales. The largest and statistically significant advantage on the Child domain in the intervention group was seen in the 'adaptability' subscale which measures a child's reactivity and self-regulation in response to emotional distress or unexpected change. Stress reactivity in infants is a specific area that is reported to be impacted negatively by maternal anxiety in pregnancy.[38] In our previous 9-month follow-up of the same cohort,[28] stress reactivity also showed a large effect size favouring the intervention group. Our current findings therefore suggest that the beneficial effects of CBT in pregnancy on stress reactivity in the offspring are maintained up until 2 years of age.

Qualitatively, the 2-year results reported here are also largely consistent with our previous report of infant developmental progress at 9 months of age. Between-group differences in motor development at 2 years showed a medium-to-large effect size favouring the intervention, which is consistent with longitudinal studies by others reporting a negative association between maternal antenatal psychological distress and child motor

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

Table 5. Summary of between-group differences in behavioural outcomes 5 years

	Intervention	TAU		
	M (*SD*)	*M* (*SD*)		
	N = 12	*N* = 12	*d*	95% CI
CBCL Total Problems	37.7 (35.5)	39.3 (32.4)	0.05	0.00 to 0.32
CBCL Anxiety/Depression	3.2 (5.3)	4.2 (4.5)	0.21	0.00 to 0.97
CBCL Somatic Complaints	1.7 (1.7)	1.3 (1.4)	0.27	−0.54 to 1.07
CBCL Withdrawn	1.8 (2.4)	3.2 (5.1)	0.36	0.00 to 1.13
CBCL Attention Problems	4.3 (4.2)	3.3 (2.7)	0.26	−0.54 to 1.06
CBCL Aggressive Behaviour	10.2 (9.3)	10.2 (8.9)	0.00	0.00 to 0.00
CBCL Internalizing Behaviour	7.8 (8.3)	11.3 (12.7)	0.32	0.00 to 1.09
CBCL Externalizing Behaviour	14.1 (13.0)	12.3 (10.3)	0.16	−0.65 to 0.96

TAU, treatment as usual; CBCL, Child Behaviour Checklist: lower scores are more favourable. Effect sizes (Cohen's *d*) are shown with corresponding 95% confidence intervals.

development up to 2 years.[16,39] Also, a non-significant trend towards a higher score on the cognitive domain of the BSID-III favouring the intervention group was seen. On the CBCL, Anxious/depressed and withdrawn behaviour showed a substantial between-group effect size which is consistent with the reports by O'Donnell *et al.*[13] of an approximately two-fold increase in prevalence rates of emotional/behavioural disorders in children and adolescents exposed to high levels of maternal prenatal anxiety or depression.

At 5-year follow-up, significant treatment effects were no longer observed. Qualitatively, for cognitive outcomes, mean scores in the intervention group trended lower than the TAU group, with only Processing Speed scores slightly favouring the intervention group. For behavioural outcomes, anxious/depressed and withdrawn behaviour again favoured the CBT group, but the effect sizes were substantially smaller compared to the effect sizes on the corresponding scales at 2-year follow-up.

Lastly, at the 5-year follow-up, we were able to demonstrate an association between higher maternal depression or anxiety at baseline and lower cognitive scores when analysing data for the entire sample. We also found increased scores on several CBCL subscales including the CBCL total problems, internalizing and externalizing behavioural subscales in the offspring, despite treatment of half the sample. At the earlier 2-year follow-up, no such association was found.

A number of possibilities could explain the different findings at 2 and 5 years.

It is likely that, by reducing symptoms of depression and anxiety in pregnancy, the concurrent biochemical processes that are activated in response to maternal depression and anxiety are ameliorated, thereby improving child neurodevelopment. However, the effect of CBT on the underlying maternal and fetal biochemical systems may have been too weak to result in a significant improvement in neurodevelopmental outcome that could be sustained in the long-term. The treatment effects on infant neurodevelopmental outcome coupled with the poor associations with baseline depression and anxiety we observed at 2 years *v*. the strong associations with baseline depression and anxiety and the absence of any treatment effect at 5 years, may suggest that treatment has short-term effects only.

Table 6. Regressions of 2-year child outcomes on baseline depression and anxiety scores in pregnancy

Dependent variables				
	Independent variables	β	*P*	R^2
Cognition – BSID-III				
	Baseline BDI-II	0.205	0.392	3.7%
	Baseline BAI	−0.222	0.356	4.4%
Language – BSID-III				
	Baseline BDI-II	0.116	0.615	1.2%
	Baseline BAI	−0.379	0.111	12.7%
Motor – BSID-III				
	Baseline BDI-II	0.297	0.193	7.8%
	Baseline BAI	−0.238	0.294	5.0%
CBCL – Total Problems				
	Baseline BDI-II	0.226	0.310	4.5%
	Baseline BAI	−0.043	0.847	0.2%
CBCL – Anxious/depressed				
	Baseline BDI-II	0.186	0.485	1.9%
	Baseline BAI	−0.145	0.389	3.1%
PSI – Adaptability				
	Baseline BDI-II	0.043	0.826	0.2%
	Baseline BAI	0.343	0.093	10.4%

BSID-III, Bayley Scales of Infant Development; CBCL, Child Behaviour Checklist; PSI, Parenting Stress Index; BDI-II, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

Alternatively, it is conceivable that our ability to measure the effects of prenatal stress on brain development might emerge gradually as infant cognitive capacity develops, and may only be detected in later life. It is also known that the prevalence of

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

Table 7. Regression of 5-year child outcomes on baseline depression and anxiety scores in pregnancy

Dependent variables						
	Independent variables	β	*P*	R^2	$P^{(adj)}$	$R^{2(adj)}$
Verbal – WPPSI-III						
	Baseline BDI-II	−0.585	0.033*	26.8%	0.075	28.1%
	Baseline BAI	−0.917	0.013*	36.6%	0.043*	36.8%
Performance – WPPSI-III						
	Baseline BDI-II	−0.533	0.116	14.7%		
	Baseline BAI	−1.042	0.014*	34.3%	0.042*	34.3%
Processing Speed – WPPSI-III						
	Baseline BDI-II	−0.084	0.796	0.5%		
	Baseline BAI	−0.409	0.355	6.6%		
Full Scale – WPPSI-III						
	Baseline BDI-II	−0.546	0.059	21.8%		
	Baseline BAI	−1.014	0.006*	42.3%	0.008*	45.4%
CBCL – Total Problems (norm)						
	Baseline BDI-II	0.013	0.251	6.2%		
	Baseline BAI	0.031	0.004*	34.9%	0.014*	41.2%
CBCL – Emotional/Reactivity						
	Baseline BDI-II	0.221	0.157	26.5%		
	Baseline BAI	0.484	0.011*	62.9%	0.017*	67%
CBCL – Anxiety/Depression						
	Baseline BDI-II	0.238	0.024*	21.9%	0.031*	25.5%
	Baseline BAI	0.335	0.010*	28.6%	0.007*	33.2%
CBCL – Somatic Complaints						
	Baseline BDI-II	0.035	0.333	4.5%		
	Baseline BAI	0.043	0.337	4.6%		
CBCL – Withdrawn Behaviour						
	Baseline BDI-II	0.148	0.101	12.3%		
	Baseline BAI	0.243	0.030*	21.4%	0.025*	24.7%
CBCL – Sleeping Problems						
	Baseline BDI-II	−0.080	0.613	3.8%		
	Baseline BAI	0.334	0.103	33.4%		
CBCL – Attention Problems						
	Baseline BDI-II	0.103	0.184	8.3%		
	Baseline BAI	0.210	0.022*	23.7%	0.432	26.2%
CBCL – Aggressive Problems						
	Baseline BDI-II	0.376	0.061	15.7%		
	Baseline BAI	0.727	0.002*	40.1%	0.022*	42.7%
CBCL – Internalizing Behaviour						
	Baseline BDI-II	0.599	0.009*	28.2%	0.011*	31.7%
	Baseline BAI	0.812	0.004*	34.7%	0.007*	36%

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

Table 7. (*Continued*)

	Dependent variables					
	Independent variables	β	*P*	R^2	$P^{(adj)}$	$R^{2(adj)}$
CBCL – Externalizing Behaviour						
	Baseline BDI-II	0.498	0.054	16.6%		
	Baseline BAI	0.937	0.002*	40.1%	0.024*	43.1%
CBCL – Social Problems						
	Baseline BDI-II	0.349	0.010*	43.7%	0.175	47.7%
	Baseline BAI	0.255	0.103	22.4%		
CBCL – Thought Problems						
	Baseline BDI-II	0.205	0.115	19.4%		
	Baseline BAI	0.204	0.144	18.3%		
CBCL – Rule Breaking Behaviour						
	Baseline BDI-II	0.240	0.032*	32.8%	0.161	33%
	Baseline BAI	0.219	0.070	26.7%		

WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence; CBCL, Child Behaviour Checklist; BDI-II, Beck Depression Inventory; BAI, Beck Anxiety Inventory.
$^{(adj)}$: adjusted for current depression or anxiety symptoms.
*$P < 0.05$.

behavioural disorders in children increases with age,[40] and the subtle programming effects of prenatal depression and anxiety might be more distinct when children grow older.

It is also possible that if the treatment was given earlier in pregnancy, it would have had a stronger or more lasting effect on child outcomes, as some studies show the strongest effects of prenatal psychosocial stress exposure on outcomes such as schizophrenia and autism occur in those children who were prenatally exposed in the first trimester of pregnancy.[41,42] A final explanation for the difference in the effect of CBT on children's neurodevelopmental outcomes at 2 and 5 years, is that a larger proportion of women from the CBT group who participated in the 2-year follow-up showed a 'successful' response to treatment (defined as a 50% reduction in depression symptom score as well as a post-treatment depression symptom score (BDI-II) of 18 points or less, indicating minimal to mild depression), compared to women who participated in the 5-year follow-up (Table 1).

Future directions – Need to explore mechanisms

The underlying pathways that 'transfer' the effects of maternal depression and anxiety on to the fetus are largely unknown, but are important to identify in order to develop effective preventive strategies. Maternal HPA axis dysregulation is likely to play a role, but there is little evidence for a direct correlation between symptoms of depression and anxiety in pregnancy and maternal plasma cortisol, indicating that additional or additive mechanisms are involved.[43,44] Epigenetic changes may be induced by antenatal depression and anxiety in fetal genes that are important for neurodevelopment.[27,45,46] Another system that may be involved in prenatal programming of neurodevelopment is the immune system, with activation of inflammatory pathways in the depressed or anxious mother with consequences for functioning of tissue macrophages in the placenta and fetal brain.[47] Also, fetal exposure to increased neurotransmitters such as serotonin may occur in women with depression, through alterations in the enzyme monoamine oxidase A, which regulates transplacental serotonin transfer.[17] These proposed mechanisms all provide potential future directions that need to be explored in further research.

Limitations

Our study also has some important limitations that need to be carefully considered when interpreting the results. The main limitation of the study is the small sample size. Effects of antenatal depression treatment on child behaviour and cognition that are too small to detect in such a small sample size may be missed, despite being clinically meaningful. Another limitation is that attrition bias is likely to have occurred, as both samples at 2 and 5 years showed a (non-significant) trend towards less severe symptoms of depression and anxiety at baseline compared to the whole study sample, which may have led to an underestimation of the effect of treatment on long-term child outcomes. Also, there was a higher reported use of medication for depression in the TAU group at both follow-up time points.

Second, unmeasured previous and postnatal episodes of depression in the women of our sample, in combination with the unhealthy behaviours associated with depression may have substantially affected neurodevelopmental outcome in the children through various mechanisms. Nevertheless, because of the experimental nature of the current study, both women from the CBT as well as the TAU group are likely to have approximately similar risk profiles, increasing the likelihood that changes seen in offspring development can be attributed to (improvements of) antenatal depression and anxiety. Also, symptoms of maternal depression and anxiety at both follow-up rounds did not differ between the TAU and CBT group (Table 1), indicating that exposure to postnatal maternal mood and associated behavioural changes was approximately similar in both groups.

Another limitation is that anxiety and depression may affect neurodevelopment both through different underlying pathways,

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

and we did not analyse their co-morbidity in relation to neurodevelopmental outcome in our sample. Another potential source of bias is the fact that most developmental and behavioural outcomes were based on maternal, and thus subjective, reports. In future studies, it would be highly informative to additionally acquire behavioural information from, for example, teachers, to gain more objective child behavioural outcome measures.

Conclusion

This was one of the first follow-up studies of an RCT assessing a treatment for antenatal depression and anxiety on cognitive and behavioural outcomes in children. Significant treatment effects were present at 2 but not at 5 years. As far as we are aware, only two published studies, by ourselves and one other group, have sought to evaluate the impact of actively treating antenatal depression on early child outcomes.[9,28] Netsi *et al.* found no effect of CBT on infant sleep behaviour and offspring temperament per se, but they did show that the decrease in symptom severity of depression was positively associated with sleep behaviour in the offspring, as well as an easier temperament, which was more pronounced in the CBT group compared to the TAU group. These findings, together with our results showing improvements in child outcomes up to 2 years highlight the importance of identification and treatment of depression and anxiety in antenatal care. During the design stage of future trials, careful attention should be paid to the most current evidence regarding the specific timing of fetal exposure to maternal antenatal emotional distress and its possible association with the emergence of particular child developmental problems at different ages.

Acknowledgements. We thank the women and children who took part in this study.

Role of the funding source. This stream of work was supported by funding from Australian Rotary Health, the MBF/BUPA foundations, the Urquhart Charitable Fund and the Austin Medical Research Foundation. The MBF/BUPA foundations funded the 2-year follow-up and the Brain and Behaviour research foundation, (NARSAD Young Investigator Grant, project 22975) funded the 5-year follow-up. The funding organizations had no role in the design and conduct of the study; collection, management, and analysis of the data; or preparation, review, and approval of the manuscript.

Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Australian Government - National Statement on Ethical Conduct in Human Research (2007)) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committee (The Human Research Ethics Committees of Northern Health, Austin Health, and Mercy Health, Melbourne, Australia).

References

1. Glover V. Maternal depression, anxiety and stress during pregnancy and child outcome: what needs to be done. *Best Pract Res Clin Obstet Gynaecol*. 2014; 28, 25–35.
2. Woody CA, Ferrari AJ, Siskind DJ, *et al.* A systematic review and meta-regression of the prevalence and incidence of perinatal depression. *J Affect Disord*. 2017; 219, 86–92.
3. Gavin NI, Gaynes BN, Lohr KN, *et al.* Perinatal depression. *Obstet Gynecol*. 2005; 106(5, Part 1), 1071–1083.
4. Dennis C-L, Falah-Hassani K, Shiri R. Prevalence of antenatal and postnatal anxiety: systematic review and meta-analysis. *Br J Psychiatry*. 2017; 210, 315–323.
5. Bauer A, Parsonage M, Knapp M. *et al.* The costs of perinatal mental health problems. Retrieved 27 March 2018 from http://eprints.lse.ac.uk/59885/1/__lse.ac.uk_storage_LIBRARY_Secondary_libfile_shared_repository_Content_Bauer%2C%20M_Bauer_Costs_perinatal_ mental_2014_-Bauer_Costs_perinatal_mental_2014_author.pdf.
6. O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. *Dev Neurosci*. 2009; 31(4), 285–292.
7. Schuurmans C, Kurrasch D. Neurodevelopmental consequences of maternal distress: What do we really know? *Clin Genet*. 2013; 83, 108–117.
8. Weinstock M. The long-term behavioural consequences of prenatal stress. *Neurosci Biobehav Rev*. 2008; 32, 1073–1086.
9. Netsi E, Evans J, Wulff K, *et al.* Infant outcomes following treatment of antenatal depression: findings from a pilot randomized controlled trial. *J Affect Disord*. 2015; 188, 252–256.
10. O'Connor TG, Heron J, Golding J. *et al.* ALSPAC Study Team. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry*. 2003; 44(7), 1025–1036.
11. Van Batenburg-Eddes T, Brion MJ, Henrichs J, *et al.* Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study. *J Child Psychol Psychiatry*. 2013; 54, 591–600.
12. Barker ED, Jaffee SR, Uher R, *et al.* The contribution of prenatal and postnatal maternal anxiety and depression to child maladjustment. *Depress Anxiety*. 2011; 28, 696–702.
13. O'Donnell KJ, Glover V, Barker ED, *et al.* The persisting effect of maternal mood in pregnancy on childhood psychopathology. *Dev Psychopathol*. 2014; 26, 393–403.
14. Van den Bergh BRH, Marcoen A. High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Dev*. 2004; 75, 1085–1097.
15. Bergman K, Sarkar P, O'connor TG, *et al.* Maternal stress during pregnancy predicts cognitive ability and fearfulness in infancy. *J Am Acad Child Adolesc Psychiatry*. 2007; 46, 1454–1463.
16. Huizink AC, Robles de Medina PG, Mulder EJH, *et al.* Stress during pregnancy is associated with developmental outcome in infancy. *J Child Psychol Psychiatry*. 2003; 44, 810–818.
17. Blakeley PM, Capron LE, Jensen AB, *et al.* Maternal prenatal symptoms of depression and down regulation of placental monoamine oxidase A expression. *J Psychosom Res*. 2013; 75, 341–345.
18. de Weerth C, Buitelaar JK, Mulder EJH. Prenatal programming of behavior, physiology and cognition. *Neurosci Biobehav Rev*. 2005; 29, 207–208.
19. Mehta D, Klengel T, Conneely KN, *et al.* Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proc Natl Acad Sci*. 2013; 110, 8302–8307.
20. Mairesse J, Lesage J, Breton C, *et al.* Maternal stress alters endocrine function of the feto-placental unit in rats. *Am J Physiol Metab*. 2007; 292, E1526–E1533.
21. O'Donnell KJ, Bugge Jensen A, Freeman L, *et al.* Maternal prenatal anxiety and downregulation of placental 11β-HSD2. *Psychoneuroendocrinology*. 2012; 37, 818–826.
22. Uno H, Eisele S, Sakai A, *et al.* Neurotoxicity of glucocorticoids in the primate brain. *Horm Behav*. 1994; 28, 336–348.
23. Coe CL, Lubach GR. Developmental consequences of antenatal dexamethasone treatment in nonhuman primates. *Neurosci Biobehav Rev*. 2005; 29, 227–235.
24. Babenko O, Kovalchuk I, Metz GAS. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. *Neurosci Biobehav Rev*. 2015; 48, 70–91.
25. Qiu A, Anh TT, Li Y, *et al.* Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. *Transl Psychiatry*. 2015; 5, e508–e508.

https://doi.org/10.1017/S2040174418000739 Published online by Cambridge University Press

26. Qiu A, Tuan TA, Ong ML, *et al*. COMT haplotypes modulate associations of antenatal maternal anxiety and neonatal cortical morphology. *Am J Psychiatry*. 2015; 172, 163–172.
27. Oberlander TF, Weinberg J, Papsdorf M, *et al*. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*. 2008; 3, 97–106.
28. Milgrom J, Holt C, Holt CJ, *et al*. Feasibility study and pilot randomised trial of an antenatal depression treatment with infant follow-up. *Arch Womens Ment Health*. 2015; 18, 717–730.
29. First MB, Spitzer RL, Gibbon M. *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P, Version 2.0)*. 1996. Am Psychiatr Press Inc: Washington, DC.
30. Beck AT, Steer RA, Brown GK. *BDI-II Manual,*. 1996. The Psychological Corporation, San Antonio: TX.
31. Milgrom J, Ericksen J, Negri L, *et al*. Screening for postnatal depression in routine primary care: properties of the Edinburgh Postnatal Depression Scale in an Australian sample. *Aust New Zeal J Psychiatry*. 2005; 39, 833–839.
32. Beck AT, Epstein, N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988; 56, 893–897.
33. Bayley N. *Bayley Scales of Infant Development*, 3rd edn, 2005. Pearson PsychCorp: San Antonio, TX.
34. Abidin RR. *Parenting Stress Index*, 4th edn, 2012. PAR, Lutz: FL.
35. Achenbach TM. *Integrative Guide for the 1991 CBCL/4-18, YSR, and TRF Profiles*. 1991. University of Vermont: Burlington, VT.
36. Wechsler D. *The Wechsler Preschool and Primary Scale of Intelligence*, 3rd edn, 2002; TX Psychol Corp: San Antonio, TX.
37. Cohen J. A power primer. *Psychol Bull*. 1992; 112, 155–159.
38. Talge NM, Neal C, Glover V, Early stress, translational research and prevention science network: fetal and neonatal experience on child and adolescent mental health. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why?. *J Child Psychol Psychiatry*. 2007; 48, 245–261.
39. Laplante DP, Barr RG, Brunet A, *et al*. Stress during pregnancy affects general intellectual and language functioning in human toddlers. *Pediatr Res*. 2004; 56, 400–410.
40. Ford T, Vostanis P, Meltzer H, *et al*. Psychiatric disorder among British children looked after by local authorities: comparison with children living in private households. *Br J Psychiatry*. 2007; 190, 319–325.
41. Rodriguez A, Bohlin G. Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? *J Child Psychol Psychiatry*. 2005; 46, 246–254.
42. Khashan AS, Abel KM, McNamee R, *et al*. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Arch Gen Psychiatry*. 2008; 65, 146–152.
43. Bleker LS, Roseboom TJ, Vrijkotte TG, *et al*. Determinants of cortisol during pregnancy – the ABCD cohort. *Psychoneuroendocrinology*. 2017; 83–, 172–181.
44. Voegtline KM, Costigan KA, Kivlighan KT, *et al*. Concurrent levels of maternal salivary cortisol are unrelated to self-reported psychological measures in low-risk pregnant women. *Arch Womens Ment Health*. 2013; 16, 101–108.
45. Cao-Lei L, de Rooij SR, King S, *et al*. Prenatal stress and epigenetics. *Neurosci Biobehav Rev*. 2017; pii, S0149-7634(16)30726-6. doi:10.1016/j.neubiorev.2017.05.016.
46. Palma-Gudiel H, Córdova-Palomera A, Eixarch E, *et al*. Maternal psychosocial stress during pregnancy alters the epigenetic signature of the glucocorticoid receptor gene promoter in their offspring: a meta-analysis. *Epigenetics*. 2015; 10, 893–902.
47. Prins JR, Eskandar S, Eggen BJL, *et al*. Microglia, the missing link in maternal immune activation and fetal neurodevelopment; and a possible link in preeclampsia and disturbed neurodevelopment? *J Reprod Immunol*. 2018; 126, 18–22.