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Postnatal maternal depressive symptoms and behavioural outcomes in term- and preterm-born toddlers

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3 **Postnatal maternal depressive symptoms and behavioural outcomes in term- and**
4 **preterm-born toddlers**
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Abstract

Objectives: To examine the association between maternal depressive symptoms in the immediate postnatal period and offspring's mental health in a large cohort of term- and preterm-born toddlers.

Design and Participants: Data were drawn from the Developing Human Connectome Project. Maternal postnatal depressive symptoms were assessed at term, and children's outcomes were evaluated at a median corrected age of 18.4 months (range 17.3 – 24.3).

Exposure and outcomes: Preterm birth was defined as <37 weeks completed gestation. Maternal depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale (EPDS). Toddlers' outcome measures were parent-rated Child Behaviour Checklist 1^{1/2}-5 Total (CBCL) and Quantitative Checklist for Autism in Toddlers (Q-CHAT) scores. Toddlers' cognition was assessed with the Bayley Scales of Infant and Toddler Development – Third Edition (Bayley-III).

Results: Higher maternal EPDS scores were associated with toddlers' higher CBCL ($B=0.93$, 95% CI 0.43-1.44, $p<0.001$, $f^2=0.05$) and Q-CHAT scores ($B=0.27$, 95% CI 0.03-0.52, $p=.031$, $f^2=0.01$). Higher maternal EPDS scores were not associated with toddlers' cognitive outcomes. Maternal EPDS, toddlers' CBCL and Q-CHAT scores did not differ between preterm ($n=97$; 19.1% of the total sample) and term participants.

Conclusions: Our findings indicate that children whose mothers had increased depressive symptoms in the early postnatal period, including subclinical symptoms, exhibit more maternally-reported behavioural problems in toddlerhood. These associations were independent of gestational age. Further research is needed to confirm the clinical significance of these findings.

Strengths and limitations of this study

- Prospective study with a large sample, using multiple imputation to reduce non-response bias.
- Maternal depressive symptoms assessed as a continuous variable, providing more nuanced information about the significance of subclinical symptoms.
- Maternal depressive symptoms assessed earlier than in previous studies, enabling recognition of early screening opportunities for families.
- Potential shared method variance bias through parent-completed child behavioural assessments.
- Unknown paternal and parental factors, such as comorbid psychiatric conditions, that may confound our findings.

Keywords

Postpartum Depression; Child Development; Autism; Mental Health; Child Behavior; Mood Disorder.

Declarations

Funding

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Conflict of interest / Competing interests

ADE received financial support from the EU-AIMS-Trials (European Research Council under the European Union Seventh Framework Programme) as co-Principal Investigator.

ADE received consulting fees from Chiesi Farmaceutici (advice on neuroprotection in newborn infants) and Medtronix (unpaid participation in scientific advice committee). ADE has a patent on Xenon as an organ protectant (No P023708WO). ADE was Chair of the Data Monitoring and Ethics Committee for the Baby-Oscar Trial, and served on the Data Monitoring and Ethics Committee for the PAEN Trial.

There are no other relationships or activities that could appear to have influenced the submitted work.

Availability of data and material

Research data will be available as part of Developing Human Connectome Project (<http://www.developingconnectome.org/>).

Code availability

Not applicable.

Ethics approval

This study was approved by the UK National Research Ethics Authority (14/LO/1169) and conducted in accordance with the World Medical Association's Code of Ethics (Declaration of Helsinki).

Consent to participate

Written informed consent was given by children's carer(s) at recruitment into the study.

Consent for publication

Not applicable.

Patient and Public Involvement statement

The current study was developed in consultation with the Weston Programme for Family Centered Research, which involves parents to define what research is valuable to them, and to allow them to lead it with support from the scientists in the Centre for the Developing Brain.

Introduction

Postnatal depression affects approximately 12% of mothers worldwide.¹ In contrast to ‘baby blues’, which is a state of emotional lability that affects between 30-80% of women in the first few days after birth and typically resolves spontaneously within two weeks,² postnatal depression is more severe and starts in the first few months post-partum¹. Stressful life events have been linked to a heightened risk of developing postnatal depression,³ with rates as high as 40% in women who give birth before term completion (i.e., preterm, < 37 gestational weeks),⁴ likely due to heightened stress associated with perinatal complications.⁵

Women with postnatal depression tend to be less responsive to their baby’s needs and to display less affection.⁶ Therefore, in the short-term postpartum depression may affect mother-infant interactions⁷ and in the long-term it may lead to alterations in brain development,⁸ emotional difficulties,⁹ less secure attachment, cognitive and behavioural problems in childhood, and a possible increased risk of autism spectrum disorder (ASD).^{10,11} Large cohort studies, such as the Avon Longitudinal Study of Parents and Children (ALSPAC), have shown that these associations are even evident when maternal depression is measured on a continuum of symptoms rather than a dichotomous diagnosis,¹²⁻¹⁴ supporting the notion that elevated sub-diagnostic psychiatric symptoms can also negatively impact on children’s development.¹⁵

Studies investigating the underlying causes that may link maternal postnatal depression to child outcomes have implicated several biological and environmental variables. For instance, genetic and epigenetic factors have been shown to both mediate and mitigate the intergenerational transmission of psychiatric disorders,¹⁶ while lower quality parenting, interparental conflict, and socioeconomic deprivation have been shown to exacerbate children’s developmental risk.¹¹ In addition, preterm birth has been associated with alterations in early brain development,¹⁷ as well as neurological, behavioural and cognitive problems in childhood and beyond.^{18,19} Therefore, it is complex to disentangle the possible effects of postnatal maternal mental health and those of perinatal clinical factors on specific outcomes in preterm children, as these may involve both maternal psychosocial and biological variables and child preterm-related neurodevelopmental morbidity. Furthermore, a question that remains unanswered is whether perinatal clinical risk accentuates the association between maternal postnatal depressive symptoms and child outcome. Previous research has proposed a diathesis-stress model, whereby preterm birth is regarded as a

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3 vulnerability factor that makes preterm infants more prone to suboptimal environmental
4 influences compared to term infants.^{20,21} On the other hand, the differential susceptibility
5 model frames preterm birth as a plasticity factor that makes infants more likely to have both
6 poorer outcomes in negative environments, as well as better outcomes in supportive
7 environments.^{21,22}
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13 Given that mothers of preterm children experience elevated levels of distress,²³ are at high
14 risk of developing postnatal depression,⁴ and that preterm children themselves are vulnerable
15 to psychiatric sequelae,²⁴ we aimed to investigate the association between very early
16 symptoms of maternal postnatal depression and child behavioural and emotional outcomes, as
17 well as whether this association was influenced by gestational age. We hypothesise that early
18 postnatal maternal depressive symptoms would be more elevated in mothers of preterm
19 compared to term infants and that these would impact preterm children's behavioural and
20 emotional outcomes to a greater degree than their term counterparts.
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29 **Methods**

30 **Sample**

31 Participants were enrolled in the Developing Human Connectome Project (DHCP,
32 <http://www.developingconnectome.org/>). Toddlers were invited to the Centre for the
33 Developing Brain, St Thomas' Hospital, London, for neurodevelopmental assessment
34 between 17 and 24 months post-expected delivery date. Inclusion criteria for our follow-up
35 study were: mother and baby attendance for magnetic resonance imaging (MRI) at term
36 corrected age; completed toddler neurodevelopmental assessment. 509 toddlers met these
37 inclusion criteria by the date of closure for this analysis (26/02/2020). This study was
38 approved by the UK National Research Ethics Authority (14/LO/1169) and conducted in
39 accordance with the World Medical Association's Code of Ethics (Declaration of Helsinki).
40 Written informed consent was given by children's carer(s) at recruitment into the study.
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51 **Maternal variables**

52 Maternal age, parity, Body Mass Index (BMI) and postcode were collected at enrolment into
53 the DHCP study. Parity was coded as 0, 1, 2, or ≥ 3 previous children. Index of Multiple
54 Deprivation (IMD) rank was computed from the current maternal postcode using the 2019
55 IMD classification,²⁵ and provided a proxy for family socioeconomic status. Lower IMD rank
56 corresponds to greater social deprivation.
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5 *Maternal depressive symptoms* were measured using the Edinburgh Postnatal Depression
6 Scale (EPDS)²⁶ at term corrected age. The EPDS is a 10-item screening questionnaire
7 completed by mothers, with higher scores reflecting a higher likelihood of depressive
8 disorders. A score of 13 can be used as a cut-off indicating high-level symptoms, although a
9 cut-off of 11 maximises the sensitivity and specificity of the screening tool for depression.²⁷

15 Child variables

16 Infant *clinical characteristics* included: sex, gestational age at birth, birth weight, and
17 pregnancy size (singleton/twin/triplet).

21
22 *Behavioural outcomes* were assessed using the Child Behaviour Checklist/1^{1/2}-5 (CBCL), a
23 parent-completed 100-item questionnaire, in which the parent rates the child's behaviour over
24 the preceding two months using a 3-point Likert scale ("not true", "somewhat or sometimes
25 true", and "very true or often true"). Responses are categorised into syndrome profiles, and
26 these are subsequently grouped into internalising (emotional reactivity, anxiety/depression,
27 somatic complaints, and withdrawal), externalising (attention problems, aggressive
28 behaviour) and total (internalising, externalising, sleep and other) problem scales. Higher
29 scores indicate increased emotional and behavioural problems. Total scores are classified into
30 a normal range ($\leq 92^{\text{rd}}$ centile, $T \leq 64$), borderline range (93^{rd} - 97^{th} centile, $T 65$ - 69), and
31 clinical range ($\geq 98^{\text{th}}$ centile, $T \geq 70$). The CBCL is known to have high reliability and validity
32 for measuring children's emotional and behavioural problems.²⁸

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43 *ASD traits* were assessed using the Quantitative Checklist for Autism in Toddlers (Q-CHAT).
44 The Q-CHAT is a parent-completed 25-item questionnaire, in which the child's behaviour is
45 scored on a 5-point (0-4) frequency scale. Higher total scores correspond to a higher
46 frequency of autistic traits. The Q-CHAT shows good test-retest reliability, face validity and
47 specificity, yet poor positive predictive value.^{29,30}

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54 *Cognitive assessment* was performed using the Bayley Scales of Infant and Toddler
55 Development – Third Edition (Bayley-III). The Bayley-III provides scores for a child's
56 overall cognitive, language and motor development. The cognitive standardised composite
57 score was used in this study; scores between 70-85 indicate mild cognitive impairment, and
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3 scores lower than 70 indicate moderate-severe impairment³¹. Reliability and validity of the
4 Bayley-III have been shown to be robust.³²
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8 Assessments were carried out by staff experienced in the neurocognitive assessments of
9 toddlers.
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13 Analysis

14 Descriptive statistics and one-way ANOVA tests were performed in IBM SPSS Statistics for
15 Windows v.25. All other analyses were carried out in Stata v.16.
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20 Multiple imputation (MI) was carried out to account for missing data in CBCL (11/509,
21 2.24%), Q-CHAT (9/509, 1.8%), maternal EPDS (73/509, 14.3%), maternal BMI (27/509,
22 5.3%) and IMD rank (3/509, 0.6%). Variables were imputed simultaneously using the ‘mi
23 impute chained’ procedure that performs imputation by chained equations. The imputation
24 models included all variables that appear in the corresponding analysis models and also had
25 the same structural form as the analysis models. They additionally included all variables
26 correlating with the incomplete variables, as well as all predictors of the probability of a
27 value being missing.³³ Maternal depression and CBCL were imputed using Poisson
28 regression; Q-CHAT, maternal BMI, and the IMD rank were imputed using linear regression.
29 40 MI datasets were created. To assess the stability of our MI parameters, we extracted the
30 Monte Carlo error of each parameter estimate and examined whether the error for the
31 coefficient was less than 10% of the parameter’s standard error estimate. MI estimates were
32 used for the primary analyses and compared to the estimates from complete-case (CC,
33 individuals who had no missing data pre-imputation) analyses. Normal probability plots of
34 residuals from the CC analyses were examined.
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48 The analysis models used multiple linear regression with standard errors that allowed for
49 intragroup correlation and were fitted using the ‘mi estimate’ procedure, which estimates
50 effects after application of Rubin’s rules.³⁴ For continuous variables, Cohen’s f-squared effect
51 sizes were calculated using $f^2 = (R_{AB}^2 - R_A^2)/(1 - R_{AB}^2)$, where R_{AB}^2 is the R-squared value
52 from a regression model that includes the variable of interest as well as all the covariates used
53 in the model, and R_A^2 is the R-squared value from the regression model that includes only the
54 covariates.^{35,36} For binary variables, Cohen’s f-squared effect sizes were produced after
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estimating first the Cohen's d using the formula: $f^2 = \frac{d}{2k}$, where k is the number of groups.

As a measure of dispersion, Cohen's d used the average root mean-square error over the MI datasets. Adjusted R-squared values after MI were extracted after estimating the model with the user-written 'mibeta' command with the 'fisherz' option,³⁷ which calculates R-squared measures for linear regression with MI data. The significance of the joint effect of the categorical variable parity was assessed using 'mi test' which performs Wald tests of composite linear hypotheses.

Primary outcome measures were children's total CBCL raw score and Q-CHAT score.

Secondary outcome measures were CBCL internalising and externalising scores. The effect of maternal EPDS score was adjusted for IMD rank, maternal age, maternal BMI, maternal parity, pregnancy size, and the following child's variables: gestational age, birth weight, Bayley-III cognitive composite score, and corrected age at assessment. The interaction between gestational age and maternal depression was explored using a complete case analysis in both CBCL and Q-CHAT models. EPDS, CBCL and Q-CHAT scores were compared between term and preterm infants using the complete case dataset.

In order to investigate the specificity of the association between maternal EPDS scores and child's behavioural outcomes (versus cognitive outcomes) we repeated the analyses using the Bayley-III cognitive composite score as primary outcome, with the following confounders: IMD rank, maternal age, maternal BMI, maternal parity, pregnancy size, and the following child's variables: gestational age, birth weight, corrected age at assessment, and Q-CHAT score. CBCL score was not included in the model predicting cognitive outcome, because cognition was not a significant predictor of CBCL (see Results).

As all mothers had their EPDS score measured near term-corrected age, we further investigated the association between time elapsing between baby's birth and mother's EPDS assessment and EPDS score, in order to avoid erroneously identifying 'baby blues' in mothers of term-born infants versus postnatal depression in mothers of preterm infants. This post-hoc analysis was performed using Poisson regression.

Results

509 toddlers were followed up at a median corrected age of 18.4 months (range 17.3 – 24.3 months). 51 (10.0%) of these were twins, and 3 (0.59%) were triplets. 21/509 (4.13%) of mothers scored above a clinical cut-off (≥ 13) on the EPDS. Demographic data are shown in Table 1. 400 (78.6%) children had complete data. Missing data were imputed and thus all 509 subjects were included in the primary and secondary analyses. One participant was excluded from the cognition analysis after examining the quintiles of the residuals against the theoretical quintiles of a normal distribution. The mean CBCL T score was 46.9 (SD 9.5) (Table 1); 484 (95.1%) of participants had a CBCL score in the normal range, 14 (2.8%) were borderline, and no participants scored in the clinical range. The mean Q-CHAT score was 30.5 (SD 9.3) (Table 1).

Predictors of children's CBCL and Q-CHAT scores after multiple imputation are shown in Table 2. Higher maternal EPDS score was associated with children's higher CBCL Total score ($B=0.93$, 95% CI 0.43-1.44, $p<0.001$, $f^2=0.05$) and Q-CHAT score ($B=0.27$, 95% CI 0.03-0.52, $p=.031$, $f^2=0.01$) (Table 2). These associations are presented graphically in Figure 1 and Figure 2, respectively. Higher maternal EPDS score was associated with both internalising ($B=0.22$, 95% CI 0.08-0.36, $p<0.01$, $f^2=0.03$) and externalising ($B=0.40$, 95% CI 0.20-0.61, $p<0.001$, $f^2=0.05$) symptoms in children (Supplementary Table 1 and 2, respectively). Comparison of the imputed model analyses to the complete-case analyses showed that results were consistent for the CBCL model (Supplementary Table 3). Comparison for the Q-CHAT model showed that maternal EPDS was a significant predictor in the imputed model, but not in the complete-case analysis (Supplementary Table 3).

Maternal EPDS scores did not differ between preterm and term groups in the complete dataset ($t(434)=0.11$, $p=0.92$). CBCL scores ($t(496)=0.95$, $p=0.34$) and Q-CHAT scores ($t(122.6)=0.50$, $p=0.62$) did not differ between preterm and term groups in the complete dataset. Maternal EPDS score did not disproportionately affect preterm children with respect to CBCL or Q-CHAT scores (Table 3).

Mothers who gave birth prematurely (<37 weeks gestation) had their EPDS score assessed on average 7.7 weeks later post-delivery than mothers who gave birth at term (preterm participants $M=8.9$ (SD 4.8), term participants $M=1.2$ (SD 1.3); $t(99.4)=15.5$, $p<.001$). The time-lag between birth and EPDS assessment did not predict maternal EPDS score, and there

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3 was no evidence of a significant interaction between gestation and birth-to-assessment time-
4 lag (Supplementary Table 4 and 5, respectively).
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8 Boys had higher CBCL and Q-CHAT scores than girls. Higher Q-CHAT scores were
9 associated with lower IMD rank (i.e., greater socio-economic deprivation) and lower Bayley-
10 III cognitive composite scores. Parity was not a significant predictor of outcome in any of the
11 models (Table 2).
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17 The mean Bayley III cognitive composite score in our sample was 100 (SD 11.4) (Table 1);
18 this corresponds to the standardised test mean.³¹ 480 (94.3%) of participants had a normal
19 cognitive score, 24 (4.7%) had mild impairment, and 5 (1%) had moderate-severe
20 impairment. Predictors of children's cognitive score are shown in Table 4. Maternal EPDS
21 score at term was not associated with toddlers' cognitive outcomes ($B=-0.22$, 95% CI -0.50-
22 0.05, $p=.108$) (Table 4).
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31 **Discussion**

32 **Principal findings**

33 Contrary to our predictions, mothers of preterm infants did not display more depressive
34 symptoms compared to mothers of term infants. Moreover, gestational age not influence the
35 association between maternal depressive symptoms and infants' behavioural outcomes in
36 toddlerhood. These results suggest that preterm birth may not be a vulnerability or plasticity
37 factor with respect to the effect of maternal postnatal depression on infants' behavioural
38 development in the first 18 months of life. However, our results do suggest that more
39 maternal self-reported depressive symptoms shortly after birth are associated with greater
40 toddlers' behavioural problems and ASD traits, but not with cognitive outcomes. Given that
41 fewer than 5% of the mothers in our cohort had EPDS scores above a clinical threshold,²⁶ our
42 findings indicate that even subclinical depressive symptoms adversely impact children's
43 behavioural outcomes. In addition, our cohort was typically developing with few CBCL
44 scores reaching a concerning threshold; our results could be interpreted within the conceptual
45 framework of mental illness lying on a continuum with typical behavioural traits.³⁸
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58 **Comparison to prior literature**

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3 The finding that more preterm infants were not disproportionately affected by maternal
4 depressive symptoms supports Hadfield et al.'s findings that maternal distress at 9 months did
5 not differentially impact very preterm (<34 weeks) or late preterm (34-36⁺⁶ weeks) infants
6 with respect to socioemotional outcomes, although paternal distress did have an impact on
7 very preterm infants' outcomes.³⁹ However, our results differ from Gueron-Sela et al.'s
8 finding that very preterm (28-33 weeks) 12 month old infants' social outcomes were more
9 influenced by maternal emotional distress at 6 months than term infants' outcomes.²² The
10 inconsistent findings may be due to methodological differences: for instance, our infant
11 assessment being conducted at 18 months corrected age when social competency is more
12 developed, our assessment of maternal depressive symptoms being in the very early postnatal
13 period, or our use of a screening measure, the Q-CHAT, as a measure of ASD traits.
14 Importantly, the lack of support for a diathesis-stress or differential susceptibility model of
15 maternal mental state on younger preterm infants in our study must be viewed in the context
16 of our results also showing no difference in CBCL and Q-CHAT scores between term and
17 preterm infants. This is in contrast to the existing literature that preterm infants are more
18 likely to develop behavioural problems, such as ADHD, in childhood and adolescence.^{19,24} It
19 is possible that the phenotypes of neurodevelopmental and neuropsychiatric disorders
20 assessed with the chosen behavioural measures may not be sufficiently expressed at 18
21 months corrected age.⁴⁰ In addition, as briefly discussed above, much of the existing literature
22 emphasises the risk of extreme (<28 weeks) or very preterm (28-33 weeks) birth on later
23 mental health outcomes,^{19,24} whereas only 3.5% and 5.5% of our participants fell within the
24 extreme and very preterm birth group, respectively, and we thus may not have the power to
25 show any subtle effects.
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45 Our results with respect to internalising and externalising behavioural outcomes are in line
46 with previous studies, including large population cohort studies, that show an association
47 between postnatal maternal depression and young children's emotional and behavioural
48 problems.¹¹ The only previous study investigating this association in infants at 18 months
49 found maternal depression to be associated with internalising and dysregulated behaviour, but
50 not externalising symptoms.⁴¹ This difference between our and Conroy et al.'s findings may
51 have arisen from their exclusion of infants born <36 weeks and their use of a clinical
52 diagnosis of depression for mothers, rather than the dimensional approach we employed.
53 Interestingly, our finding that even subclinical depressive symptoms may adversely impact
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3 children's behavioural outcomes is in line with recent data showing that low- as well as high-
4 level depressive symptoms are associated with internalising and externalising symptoms in
5 children aged 3 years.⁴²
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10 The results showing an association between maternal postnatal depressive symptoms and
11 childhood ASD are less robust and need to be interpreted with caution. Although some prior
12 studies have reported an association between antenatal maternal depression and offspring's
13 ASD,^{10,43} and postnatal depression has been suggested as a potential focus of cross-domain
14 studies of ASD,⁴⁴ there is no clear aetiological role of maternal postnatal depression in the
15 development of ASD *per se*. Also, given that mothers with ASD are more likely to suffer
16 from perinatal depression than mothers without ASD,⁴⁵ and ASD is highly heritable,⁴⁶
17 maternal depression may be a confounder in our observed results.
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26 **Strengths & limitations of the study**

27 The strengths of this study lie primarily in its large sample and prospective data collection.
28 Moreover, the use of multiple imputation methodology has facilitated retention of a complete
29 dataset, thus minimising non-response bias and increasing parameter precision. A strength in
30 comparison to prior population cohort studies is that we assessed very early maternal
31 depressive symptoms. Given the complex interplay of biological and environmental factors in
32 the aetiology of mental health disorders, the inclusion of a substantive proportion of preterm
33 infants in our cohort also offers an important insight into the role of preterm birth in
34 influencing mental health outcomes; moreover, our results represent the full gestational
35 spectrum, rather than discrete gestational categories. In addition, using maternal depression as
36 a continuous, rather than dichotomous, variable allows a more nuanced understanding of the
37 role maternal postnatal depressive symptoms may play in influencing children's outcomes.
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48 There are five main limitations to this study. Firstly, differences in birth-to-EPDS-assessment
49 time-lags are a potential confounder, given the time-sensitive nature of early-onset temporary
50 baby blues and later-onset pathological postnatal depression. Mothers of infants born at term
51 were assessed early post-delivery, within the period one would anticipate baby blues to
52 present, whereas mothers of preterm participants were on average assessed later, when
53 postnatal depression predominates.^{1,2} Although our post-hoc analyses showed no association
54 between the time elapsed from birth to EPDS assessment and maternal EPDS score,
55 providing reassurance that our assessments of mothers of term-born infants were not inflated
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3 by the common, temporary symptoms of baby blues, it is however possible that we did not
4 capture the full extent of later-onset depressive symptoms in mothers of term-born infants.
5 This may explain why maternal EPDS scores did not differ between preterm and term groups
6 in our complete dataset analysis, contrary to the current literature.²³ Secondly, a number of
7 important confounders that are likely to affect children's behavioural outcomes were not
8 assessed in this study, including genetic risk for psychiatric disorders,⁴⁷ parental psychiatric
9 co-morbidities,⁴¹ chronicity of postnatal depressive symptoms,⁴² antenatal maternal
10 depression, paternal depression and subsequent parent-infant attachment, and inter-parental
11 conflict.¹¹ In this study we did not systematically collect maternal psychiatric history and our
12 focus was on symptoms rather than a diagnosis of depression. Thus, we are unable to
13 conclude whether our observed associations between early postnatal maternal depressive
14 symptoms and children's mental health outcomes are moderated or mediated by other
15 parental factors. Thirdly, whilst our study included a substantive proportion of preterm
16 infants (97/509, 19%), the sample was not random, as preterm children were selectively
17 recruited for the DHCP; indeed, preterm infants are over-represented in our sample when
18 compared to the UK population incidence (7.3%),⁴⁸ which may limit the study's
19 generalisability to the general population. Fourthly, the effect sizes of the association between
20 maternal EPDS score and behavioural problems and ASD traits, respectively, were small; this
21 raises questions regarding the clinical significance of our findings and potentially explains
22 some of the inconsistency between this and previous studies. Even within our analyses, the
23 association between maternal depressive symptoms and ASD traits was not observed in our
24 complete case analysis, thus calling into question the validity of this result. It is also
25 important to highlight the continuum of ASD traits that are conceptualised by the Q-CHAT,²⁹
26 as well as its poor positive predictive value;³⁰ the presence of traits does not imply a
27 diagnosis of ASD, and this distinction may also explain the contrast to previous studies.
28 Fifthly, the outcome measures used in this study were parent-completed questionnaires and it
29 is possible that reporting bias with shared method variance may have skewed our results, as
30 maternal depression has been shown to influence reporting of ASD traits,⁴⁹ including the Q-
31 CHAT,⁵⁰ and CBCL scores.⁵¹

54 **Implications of our findings**

55 Of greatest importance to clinicians and policymakers is our finding that even *subclinical*
56 maternal depressive symptoms are associated with behavioural outcomes of offspring. This
57 has significant implications for the risk-stratification of women and their babies in the
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3 postnatal period, during which contact with medical professionals is already established.
4 Identifying high risk families and providing appropriate supportive measures at the early
5 postnatal stage may help to prevent future psychiatric morbidity.
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10 **Future research**

11 Further follow-up of large cohorts of preterm and term infants, to an age when behavioural
12 phenotypes may become more pronounced, is needed to investigate whether the long-term
13 developmental trajectories of term and ex-preterm infants are differentially susceptible to
14 changes of postnatal maternal mental health. Such follow-up should use independent,
15 objective assessments of child behavioural outcomes. Further study is also needed to
16 elucidate the role of maternal depression in the aetiology of ASD, controlling for both
17 diagnostic and sub-clinical maternal ASD symptomatology. Finally, it is crucial for future
18 research to elucidate the interplay of biochemical and neurodevelopmental changes that may
19 mediate and confound the translation of environmental exposures into distal behavioural
20 phenotypes.
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31 **Conclusion**

32 This prospective longitudinal cohort study found no evidence to support the concept of
33 preterm birth as a vulnerability or plasticity factor with respect to the effect of maternal
34 depressive symptoms on behavioural development. However, we do show that early
35 subclinical maternal postnatal depressive symptoms are associated with behavioural problems
36 in children. This adds to the increasing body of literature indicating the role of subclinical and
37 early postnatal depressive symptoms in the aetiology of childhood mental health disorders.
38 These findings are of great relevance to child and public health, and have potentially
39 significant implications for developing strategies to facilitate effective screening and support
40 for women and children, enabling all to reach their full potential.
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Investigation: SF, AC; **Data curation:** IK, AL; **Formal analysis:** IK, GV, AP, CN;
Writing – original draft preparation: IK; **Writing – Review & Editing:** GV, AL, SF, AC,
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Table 1: Socio-demographic, maternal and clinical characteristics (n=509)

Variable	Number (%)*
Sex: Male	274 (53.8)
Index of Multiple Deprivation (IMD) quintiles	
1 (least deprived) ^a	65 (12.8)
2	87 (17.2)
3	108 (21.3)
4	173 (34.2)
5 (most deprived)	73 (14.4)
Gestational age at birth (weeks), median [range]	39.7 [20 – 43]
Gestational category	
Preterm (<37 weeks)	97 (19.1)
Term (≥37 weeks)	412 (80.9)
Birthweight (g), median [range]	3290 [450 – 4750]
Multiple pregnancy	54 (10.6)
Maternal parity	
0	332 (65.2)
1	124 (24.4)
2	32 (6.3)
3+	21 (4.2)
Maternal BMI (kg/m ²), median [range]	23.2 [15.3 – 43.6]
Maternal age at infant's birth (years), mean (SD)	34.2 (4.8)
Bayley III cognitive composite score, mean (SD)	100 (11.4)
CBCL total T score, mean (SD)	46.9 (9.5)
Q-CHAT total score, mean (SD)	30.5 (9.3)
EPDS score, median [range]	4 [0 – 28]

^a Quintile 1 corresponds to the highest, least deprived, IMD rankings.

* unless otherwise specified

Table 2: CBCL and Q-CHAT model predictors using multiple imputation without interaction. (Cf. Supplementary Table 3 for complete case analysis)

	CBCL			Q-CHAT		
	B [95%CI]	p	f ²	B [95%CI]	p	f ²
Maternal EPDS	0.93 [0.43, 1.44]	<.001 ***	0.05	0.27 [0.03, 0.52]	.031 *	0.01
Maternal BMI	-0.09 [-0.44, 0.26]	.621	-	0.06 [-0.13, 0.24]	.538	-
Multiple pregnancy	3.15 [-3.07, 9.37]	.320	-	1.33 [-2.62, 5.28]	.509	-
Parity						
1	-2.52 [-5.96, 0.93]	.151	-	-2.14 [-4.02, -0.27]	.025 ^a	-
2	-3.23 [-9.16, 2.70]	.285	-	0.88 [-1.99, 3.75]	.548	-
3+	-1.37 [-8.36, 5.61]	.699	-	-0.49 [-4.57, 3.60]	.815	-
IMD rank	-1.48 [-3.33, 0.37]	.117	-	-1.50 [-2.60, -0.40]	.008 **	0.02
Gestational age at birth (weeks)	0.10 [-0.65, 0.85]	.786	-	0.26 [-0.17, 0.70]	.233	-
Birthweight (kg)	0.56 [-2.65, 3.78]	.731	-	-1.24 [-2.93, 0.46]	.151	-
Sex:female	-4.14 [-6.96, -1.31]	.004 **	0.06	-1.95 [-3.42, -0.48]	.009 **	0.05
Corrected age at assessment (months)	-0.90 [-2.17, 0.37]	.166	-	-0.16 [-0.91, 0.59]	.677	-
Cognition	-0.05 [-0.20, 0.09]	.467	-	-0.27 [-0.35, -0.20]	<.001 ***	0.12

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL model adjusted R² = 0.0676. Q-CHAT model adjusted R² = 0.193.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-corrected age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

^a Wald test of whole parity variable in Q-CHAT model: F(3, 476.9) = 1.88, p = .133

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.[25]

- indicates data not given, as predictor not significant to 0.05.

Table 3: CBCL and Q-CHAT model predictors using complete case analysis with interaction of ‘EPDS x term’.

	CBCL		Q-CHAT	
	B [95%CI]	p	B [95%CI]	p
Maternal EPDS	0.89 [-0.24, 2.02]	.121	0.24 [-0.28, 0.75]	.365
Maternal BMI	-0.01 [-0.39, 0.37]	.955	0.00 [-0.16, 0.17]	.982
Multiple pregnancy	1.76 [-6.65, 10.17]	.681	0.97 [-2.07, 4.01]	.532
Parity				
1	-2.75 [-6.49, 0.99]	.149	-1.42 [-3.30, 0.46]	.139
2	-3.49 [-10.36, 3.37]	.317	0.16 [-2.84, 3.16]	.917
3+	-1.17 [-9.69, 7.35]	.788	-1.13 [-4.24, 1.98]	.476
IMD rank	-1.41 [-3.54, 0.73]	.195	-1.68 [-2.64, -0.72]	.001 **
Gestation: term	1.25 [-8.34, 10.85]	.797	2.64 [-1.74, 7.02]	.236
Birthweight (kg)	-1.01 [-4.08, 2.05]	.516	-2.25 [-3.73, -0.78]	.003 **
Sex: female	-4.64 [-7.83, -1.44]	.005 **	-2.22 [-3.72, -0.71]	.004 **
Corrected age at assessment (months)	-0.83 [-2.27, 0.62]	.261	-0.39 [-1.18, 0.04]	.335
Cognition	-0.03 [-0.20, 0.14]	.720	-0.22 [-0.29, -0.15]	<.001 ***
EPDS x gestation:term	-0.01 [-1.30, 1.28]	.991	-0.02 [-0.60, 0.56]	.950

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL model adjusted R² = 0.0865. Q-CHAT model adjusted R² = 0.215.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-corrected age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Gestation: term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months. EPDS x gestation:term = interaction term between maternal EPDS score and term gestation at birth.

Table 4: Cognition model predictors using multiple imputation.

	B [95%CI]	p
Maternal EPDS	-0.22 [-0.50, 0.05]	.108
Maternal BMI	-0.32 [-0.52, -0.13]	.001 **
Multiple pregnancy	1.65 [-2.49, 5.79]	.433
Parity		
1	-0.46 [-2.67, 1.76]	.686
2	-3.47 [-6.69, -0.25]	.035 ^a
3+	-4.57 [-9.53, 0.40]	.072
IMD rank	1.43 [0.37, 2.50]	.009 **
Gestational age at birth (weeks)	0.45 [-0.07, 0.96]	.091
Birthweight (kg)	0.81 [-1.24, 2.87]	.436
Sex: female	1.99 [0.24, 3.74]	.026 *
Corrected age at assessment (months)	-0.75 [-1.59, 0.08]	.075
Q-CHAT score	-0.39 [-0.50, -0.28]	<.001 ***

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.231

B = unstandardised coefficient.

Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-corrected age.

Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months. Q-CHAT score = infant's Q-CHAT score at 18 month assessment.

^a Wald test of whole parity variable in cognition model: F(3, 482.9)=2.41, p=0.067

Fig.1 Children's predicted CBCL scores at 18 months are positively correlated to the maternal EPDS score at term corrected age

Fig.2 Children's predicted Q-CHAT scores at 18 months are positively correlated to the maternal EPDS score at term corrected age

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3 **Supplemental material**
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5 **Supplementary Table 1:** CBCL internalising symptom model predictors using multiple imputation
6

7 **Supplementary Table 2:** CBCL externalising symptom model predictors using multiple imputation
8

9 **Supplementary Table 3:** CBCL and Q-CHAT model predictors using complete case analysis without interaction.
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11 **Supplementary Table 4:** EPDS score predictors
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13 **Supplementary Table 5:** EPDS score predictors including interaction 'term x time-lag'
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Supplementary Table 1: CBCL internalising symptom model predictors using multiple imputation

	B [95%CI]	p	f²
Maternal EPDS	0.22 [0.08, 0.36]	.003 **	0.03
Maternal BMI	-0.04 [-0.13, 0.06]	.436	-
Multiple pregnancy	0.58 [-1.10, 2.27]	.497	-
Parity			
1	-0.37 [-1.41, 0.67]	.487	-
2	-1.33 [-3.09, 0.42]	.136	-
3+	0.64 [-1.34, 2.62]	.524	-
IMD rank	-0.41 [-0.91, 0.10]	.115	-
Gestational age at birth (weeks)	0.22 [-0.00, 0.44]	.053	-
Birthweight (kg)	-0.97 [-1.90, -0.05]	.038 *	0.005
Sex: female	-0.51 [-1.35, 0.33]	.232	-
Corrected age at assessment (months)	0.02 [-0.41, 0.45]	.923	-
Cognition	-0.05 [-0.10, -0.01]	.016 *	0.01

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.0566.

B = unstandardised coefficient.

Outcome variable = Child Behaviour Checklist internalising sub-score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-corrected age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.¹

- indicates data not given, as predictor not significant to 0.05.

Supplementary Table 2: CBCL externalising symptom model predictors using multiple imputation

	B [95%CI]	p	f²
Maternal EPDS	0.40 [0.20, 0.61]	<.001 ***	0.05
Maternal BMI	0.01 [-0.17, 0.15]	.933	-
Multiple pregnancy	2.51 [-0.29, 5.31]	.079	-
Parity			
1	-1.06 [-2.53, 0.42]	.160	-
2	-0.61 [-3.55, 2.33]	.682	-
3+	-0.96 [-4.47, 2.56]	.593	-
IMD rank	-0.24 [-1.11, 0.63]	.585	-
Gestational age at birth (weeks)	-0.07 [-0.40, 0.27]	.701	-
Birthweight (kg)	1.03 [-0.38, 2.44]	.153	-
Sex: female	-1.80 [-3.07, -0.53]	.006 **	0.06
Corrected age at assessment (months)	-0.40 [-0.95, 0.16]	.161	-
Cognition	0.03 [-0.03, 0.10]	.322	-

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.0612.

B = unstandardised coefficient.

Outcome variable = Child Behaviour Checklist externalising sub-score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-corrected age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.¹

- indicates data not given, as predictor not significant to 0.05.

Supplementary Table 3: CBCL and Q-CHAT model predictors using complete case analysis without interaction.

	CBCL		Q-CHAT	
	B [95%CI]	p	B [95%CI]	p
Maternal EPDS	0.88 [0.35, 1.41]	.001 **	0.21 [-0.02, 0.44]	.069
Maternal BMI	-0.01 [-0.38, 0.37]	.963	0.01 [-0.16, 0.17]	.930
Multiple pregnancy	1.50 [-6.87, 9.87]	.724	0.43 [-2.50, 3.37]	.772
Parity				
1	-2.83 [-6.60, 0.94]	.141	-1.54 [-3.41, 0.34]	.108
2	-3.49 [-10.3, 3.35]	.316	0.13 [-2.85, 3.10]	.933
3+	-1.38 [-10.0, 7.30]	.755	-1.43 [-4.50, 1.64]	.360
IMD rank	-1.44 [-3.56, 0.67]	.181	-1.75 [-2.70, -0.79]	<.001 ***
Gestational age at birth (weeks)	0.01 [-0.90, 0.91]	.987	0.10 [-0.33, 0.54]	.639
Birthweight (kg)	-0.65 [-4.38, 3.08]	.733	-1.81 [-3.63, 0.00]	.050
Sex: female	-4.57 [-7.82, -1.31]	.006 **	-2.12 [-3.60, -0.64]	.005 **
Corrected age at assessment (months)	-0.84 [-2.26, 0.59]	.247	-0.41 [-1.18, 0.35]	.290
Cognition	-0.03 [-0.20, 0.13]	.689	-0.23 [-0.30, -0.15]	<.001 ***

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL adjusted $R^2 = 0.0862$. Q-CHAT adjusted $R^2 = 0.2103$.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist externalising sub-score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-corrected age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Gestation (weeks) = dummy variable: 34-36+6 weeks and ≥ 37 weeks gestation at birth. Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Supplementary Table 4: EPDS score predictors

	IRR [95%CI]	p
Time-lag (weeks)	1.01 [0.97, 1.05]	.647
Gestation:term	0.91 [0.64, 1.31]	.627
IMD rank	1.00 [1.00, 1.00]	.103
Multiple pregnancy	0.66 [0.46, 0.96]	.031 *
Parity		
1	0.79 [0.66, 0.95]	.011 *
2	0.87 [0.60, 1.28]	.491
3+	0.84 [0.54, 1.31]	.445
Birthweight (kg)	0.98 [0.83, 1.17]	.847
Sex:female	1.13 [0.98, 1.31]	.098

p<0.05 *; p<0.01 **; p<0.001 ***

Pseudo R² = 0.0228

IRR = incidence rate ratio

Outcome variable = maternal Edinburgh Postnatal Depression Scale (EPDS) score at term-corrected age. Time-lag (weeks) = time in weeks between birth and EPDS assessment. Gestation:term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren).

Supplementary Table 5: EPDS score predictors including interaction ‘term x time-lag’

	IRR [95%CI]	p
Time-lag (weeks)	1.00 [0.97, 1.04]	.823
Gestation: term	0.88 [0.58, 1.34]	.553
IMD rank	1.00 [1.00, 1.00]	.104
Multiple pregnancy	0.66 [0.46, 0.96]	.029 *
Parity		
1	0.79 [0.66, 0.95]	.010 *
2	0.87 [0.60, 1.28]	.480
3+	0.85 [0.55, 1.31]	.458
Birthweight (kg)	0.97 [0.83, 1.15]	.756
Sex:female	1.13 [0.98, 1.30]	.100
Term x time-lag (weeks)	1.01 [0.94, 1.10]	.735

p<0.05 *; p<0.01 **; p<0.001 ***

Pseudo R² = 0.0230

IRR = incidence rate ratio

Outcome variable = maternal Edinburgh Postnatal Depression Scale (EPDS) score at term-corrected age. Time-lag (weeks) = time in weeks between birth and EPDS assessment. Gestation: term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Term x time-lag (weeks): interaction term between term gestation at birth and time-lag between birth and maternal EPDS assessment.

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3 **Supplemental reference list**
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- 5 1. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. L. Erlbaum Associates; 1988.
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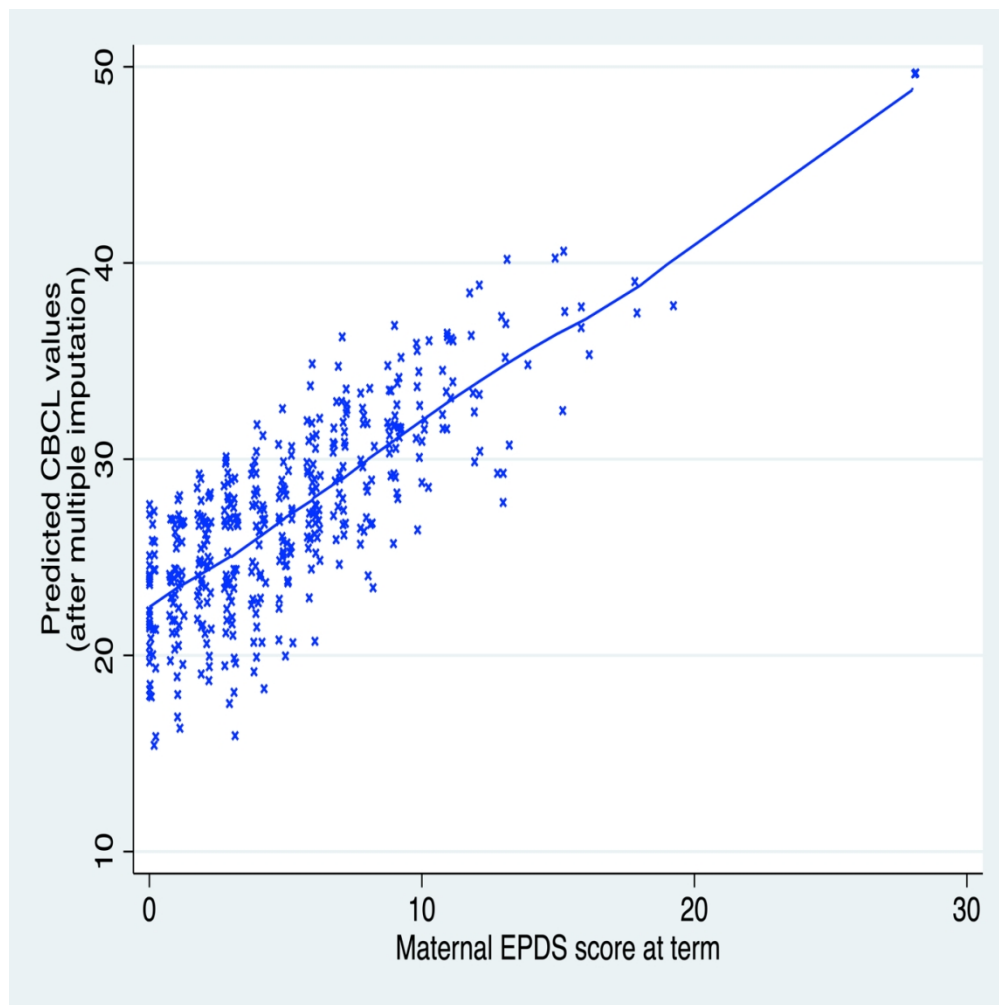


Fig.1 Children’s predicted CBCL scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age

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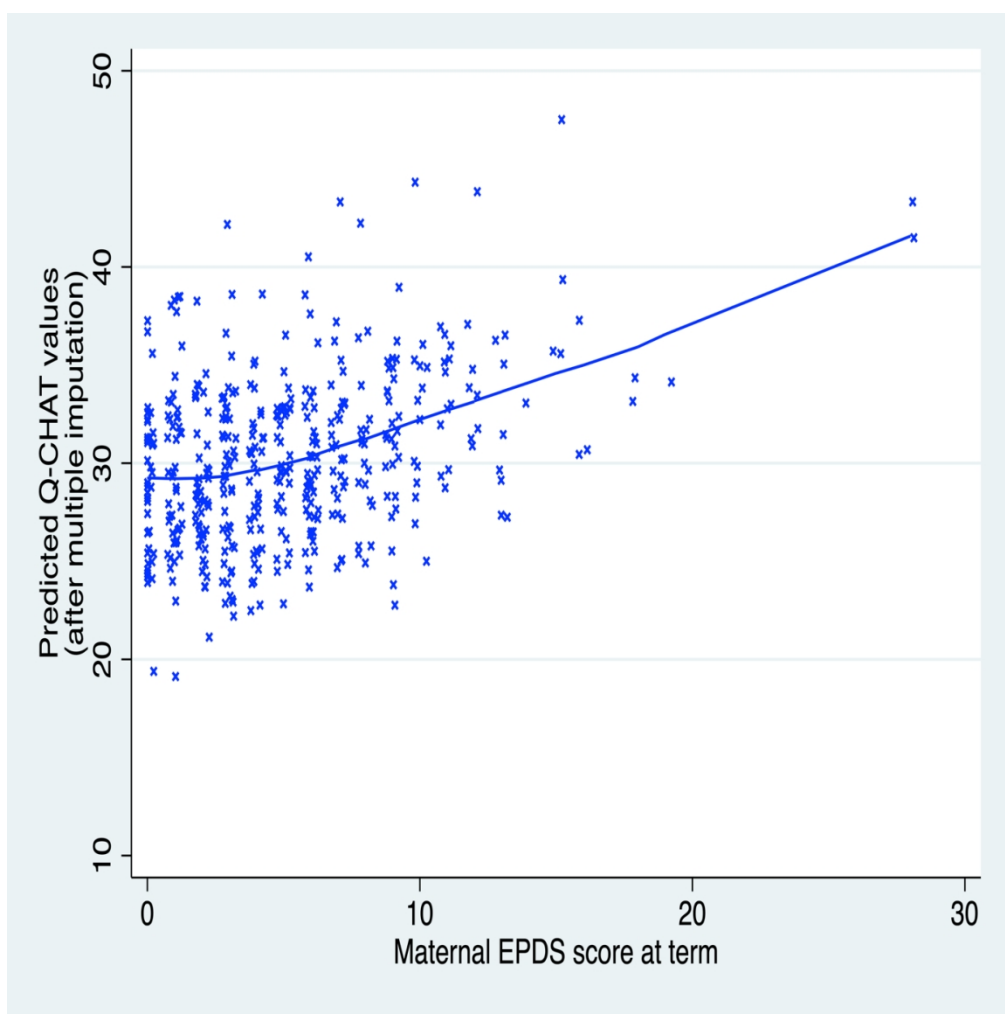


Fig.2 Children’s predicted Q-CHAT scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age.

158x158mm (220 x 220 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	1, 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
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	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
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
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
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	8, 9
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	10
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)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10

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	10
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 11
6	Discussion			
7	Key results	18	Summarise key results with reference to study objectives	11
8	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	13, 14
9	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 15
10	Generalisability	21	Discuss the generalisability (external validity) of the study results	14
11	Other information			
12	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	3

*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

Postnatal maternal depressive symptoms and behavioural outcomes in term- and preterm-born toddlers: a longitudinal UK community cohort study.

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Paediatrics
Keywords:	MENTAL HEALTH, Child & adolescent psychiatry < PSYCHIATRY, Developmental neurology & neurodisability < PAEDIATRICS, Depression & mood disorders < PSYCHIATRY, NEONATOLOGY

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3 **Postnatal maternal depressive symptoms and behavioural outcomes in term- and**
4 **preterm-born toddlers: a longitudinal UK community cohort study.**
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Abstract

Objectives: To examine the association between maternal depressive symptoms in the immediate postnatal period and offspring's behavioural outcomes in a large cohort of term- and preterm-born toddlers.

Design and Participants: Data were drawn from the Developing Human Connectome Project. Maternal postnatal depressive symptoms were assessed at term-equivalent age, and children's outcomes were evaluated at a median corrected age of 18.4 months (range 17.3 – 24.3).

Exposure and outcomes: Preterm birth was defined as <37 weeks completed gestation. Maternal depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale (EPDS). Toddlers' outcome measures were parent-rated Child Behaviour Checklist 1^{1/2}-5 Total (CBCL) and Quantitative Checklist for Autism in Toddlers (Q-CHAT) scores. Toddlers' cognition was assessed with the Bayley Scales of Infant and Toddler Development – Third Edition (Bayley-III).

Results: Higher maternal EPDS scores were associated with toddlers' higher CBCL (B=0.93, 95% CI 0.43-1.44, p<0.001, f²=0.05) and Q-CHAT scores (B=0.27, 95% CI 0.03-0.52, p=.031, f²=0.01). Higher maternal EPDS scores were not associated with toddlers' cognitive outcomes. Maternal EPDS, toddlers' CBCL and Q-CHAT scores did not differ between preterm (n=97; 19.1% of the total sample) and term participants.

Conclusions: Our findings indicate that children whose mothers reported increased depressive symptoms in the early postnatal period, including subclinical symptoms, exhibit more parent-reported behavioural problems in toddlerhood. These associations were independent of gestational age. Further research is needed to confirm the clinical significance of these findings.

Strengths and limitations of this study

- Prospective study with a large sample, using multiple imputation to reduce non-response bias.
- Maternal depressive symptoms assessed as a continuous variable, providing more nuanced information about the significance of subclinical symptoms.
- Maternal depressive symptoms assessed earlier than in previous studies, enabling recognition of early screening opportunities for families.
- Potential common method variance bias through parent-completed child behavioural assessments.
- Unknown paternal and parental factors, such as comorbid psychiatric conditions, that may confound our findings.

Keywords

Postpartum Depression; Child Development; Autism; Mental Health; Child Behavior; Mood Disorder; Preterm Birth.

Declarations

Funding

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Conflict of interest / Competing interests

ADE received financial support from the EU-AIMS-Trials (European Research Council under the European Union Seventh Framework Programme) as co-Principal Investigator.

ADE received consulting fees from Chiesi Farmaceutici (advice on neuroprotection in newborn infants) and Medtronix (unpaid participation in scientific advice committee). ADE has a patent on Xenon as an organ protectant (No P023708WO). ADE was Chair of the Data Monitoring and Ethics Committee for the Baby-Oscar Trial, and served on the Data Monitoring and Ethics Committee for the PAEN Trial.

There are no other relationships or activities that could appear to have influenced the submitted work.

Availability of data and material

Research data are available upon reasonable request.

Code availability

Not applicable.

Ethics approval

This study was approved by the UK National Research Ethics Authority (14/LO/1169) and conducted in accordance with the World Medical Association's Code of Ethics (Declaration of Helsinki).

Consent to participate

Written informed consent was given by children's carer(s) at recruitment into the study.

Consent for publication

Not applicable.

Introduction

Postnatal depression affects approximately 12% of mothers worldwide.¹ In contrast to ‘baby blues’, which is a state of emotional lability that affects between 13.7%-76.0% of women in the first few days after birth and typically resolves spontaneously within two weeks,² postnatal depression is more severe and starts in the first few months post-partum¹. Stressful life events have been linked to a heightened risk of developing postnatal depression;³ for example, mothers of preterm infants have a significantly higher risk of postpartum depression compared to mothers of term infants,⁴ likely due to heightened stress associated with perinatal complications.⁵

Women with postnatal depression tend to be less responsive to their baby’s needs and to display less affection.⁶ Therefore, in the short-term postpartum depression may affect mother-infant interactions⁷ and in the long-term it may lead to alterations in brain development,⁸ emotional difficulties,⁹ less secure attachment, cognitive and behavioural problems in childhood, and a possible increased risk of autism spectrum disorder (ASD).^{10,11} Large cohort studies, such as the Avon Longitudinal Study of Parents and Children (ALSPAC), have shown that these associations are even evident when maternal depression is measured on a continuum of symptoms rather than a dichotomous diagnosis,¹²⁻¹⁴ supporting the notion that elevated sub-diagnostic psychiatric symptoms can also negatively impact on children’s development.¹⁵

Studies investigating the underlying causes that may link maternal postnatal depression to child outcomes have implicated several biological and environmental variables. For instance, genetic and epigenetic factors have been shown to both mediate and mitigate the intergenerational transmission of psychiatric disorders,¹⁶ while lower quality parenting, interparental conflict, and socioeconomic deprivation have been shown to exacerbate children’s developmental risk of emotional and behavioural problems.¹¹ In addition, being born preterm (i.e. <37 weeks’ gestation) has been associated with alterations in early brain development,¹⁷ as well as neurological, behavioural and cognitive problems in childhood and beyond.^{18,19} Therefore, it is complex to disentangle the possible effects of postnatal maternal mental health and those of perinatal clinical factors on specific outcomes in preterm children, as these may involve both maternal psychosocial and biological variables, as well as child preterm-related neurodevelopmental morbidity.

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3 Furthermore, a question that remains unanswered is whether preterm birth accentuates the
4 association between maternal postnatal depression and child outcome. Two theoretical
5 frameworks exist that hypothesise certain infants may be influenced differently by external
6 stimuli: the diathesis stress model proposes that certain vulnerability factors make affected
7 infants more prone to suboptimal environmental influences with subsequent poorer
8 outcomes,^{20,21} whereas the differential susceptibility model frames such factors as plasticity-
9 mediating, thus leading to poorer outcomes in negative environments, as well as better
10 outcomes in supportive environments.^{21,22} Previous studies investigating differential
11 susceptibility have shown mixed findings studying a range of environmental and clinical
12 exposures,^{24,27} with child outcomes including attachment, internalising and externalising
13 behaviour, and academic competence.²⁷ Both low birthweight in term infants (small for
14 gestational age)²³ and preterm birth^{22,24,25} have been explored as distinct potential
15 susceptibility factors, as the pathophysiological mechanisms underlying their respective
16 differential susceptibility effects may differ.²⁶

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29 Given that mothers of preterm children experience elevated levels of distress,²⁸ are at high
30 risk of developing postnatal depression,²⁹ and that preterm children themselves are vulnerable
31 to psychiatric sequelae,³⁰ we aimed to investigate the association between very early
32 symptoms of maternal postnatal depression and child behavioural and emotional outcomes,
33 including ASD symptoms. No studies to date have investigated the interactive effect of
34 preterm birth and maternal depression on outcomes, hence we also aimed to explore whether
35 maternal depression had a differential effect on term and preterm children's behavioural
36 outcomes. We specifically aimed to investigate the continuum of maternal depressive
37 symptoms rather than solely focussing on clinically significant maternal depression, so as to
38 provide more nuanced information about the importance of subclinical depressive symptoms
39 on child outcomes. We hypothesised that early postnatal maternal depressive symptoms
40 would be more elevated in mothers of preterm compared to term infants and that these would
41 impact preterm children's behavioural and emotional outcomes to a greater degree than their
42 term counterparts.

54 55 **Methods**

56 **Sample**

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58 Participants were enrolled in the Developing Human Connectome Project (DHCP,
59 <http://www.developingconnectome.org/>), a neuroimaging-focused project, with eligibility
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3 criteria including pregnant women (aged ≥ 16 years) with a gestational age of 20–42 weeks,
4 and newborn infants aged 24–44 weeks; infants enrolled in the DHCP had magnetic
5 resonance imaging (MRI) at term-equivalent age. Exclusion criteria for the DHCP included:
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8 contraindications to MRI, babies being too unwell to tolerate a scan, and language difficulties
9 preventing informed consent.³¹ Toddlers were invited to the Centre for the Developing Brain,
10 St Thomas' Hospital, London, for neurodevelopmental assessment at 18 months post-
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12 expected delivery date; appointments were made according to family availability as close as
13 possible to this time-point. Inclusion criteria for our follow-up study were: mother and baby
14 attendance for MRI at term-equivalent age; completed toddler neurodevelopmental
15 assessment. These inclusion criteria were met by 509 toddlers by the date of closure for this
16 analysis (26/02/2020). Of the 509 toddlers, 51 were one of a twin pregnancy, and three were
17 one of a triplet pregnancy; the sample contained 22 sibling pairs and one set of triplets. This
18 study was approved by the UK National Research Ethics Authority (14/LO/1169) and
19 conducted in accordance with the World Medical Association's Code of Ethics (Declaration
20 of Helsinki). Written informed consent was given by children's carer(s) at recruitment into
21 the study.
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32 Maternal variables

34 Maternal age, parity, Body Mass Index (BMI) and postcode were collected at enrolment into
35 the DHCP study. Parity was coded as 0, 1, 2, or ≥ 3 previous children. Index of Multiple
36 Deprivation (IMD) rank was computed from the current maternal postcode using the 2019
37 IMD classification; it combines locality-specific information about income, employment,
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39 IMD classification; it combines locality-specific information about income, employment,
40 education, health, crime, housing and living environment, thus providing a proxy for family
41 socioeconomic status.³² Lower IMD rank corresponds to greater social deprivation.
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46 *Maternal depressive symptoms* were measured using the Edinburgh Postnatal Depression
47 Scale (EPDS)³³ on the day of infant's MRI at term-equivalent age. Mothers of infants born at
48 term were tested in the first few weeks postnatally, whereas mothers of preterm-born infants
49 were tested once they reached term-corrected age. The EPDS is a 10-item screening
50 questionnaire completed by mothers, with higher scores reflecting a higher likelihood of
51 depressive disorders. A score of 13 can be used as a cut-off indicating high-level symptoms,
52 although a cut-off of 11 maximises the sensitivity and specificity of the screening tool for
53 depression.³⁴ Mothers completed the EPDS independently in a private room in our Centre,
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55 with no interaction with the researcher. Participants were informed that the results would be
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3 discussed with them, and consented to information being shared with their General
4 Practitioner in the case of high scores. The EPDS questionnaire was scored by a member of
5 the DHCP team.³¹
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10 Child variables

11 Infant *clinical characteristics* were gathered from clinical notes where available, or from
12 maternal report, and included: sex, gestational age at birth, birth weight, and pregnancy size
13 (singleton/twin/triplet).
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18 *Behavioural outcomes* were assessed using the Child Behaviour Checklist/1^{1/2}-5 (CBCL), a
19 parent-completed 100-item questionnaire, in which the parent rates the child's behaviour over
20 the preceding two months using a 3-point Likert scale ("not true", "somewhat or sometimes
21 true", and "very true or often true"). Responses are categorised into syndrome profiles, and
22 these are subsequently grouped into internalising (emotional reactivity, anxiety/depression,
23 somatic complaints, and withdrawal), externalising (attention problems, aggressive
24 behaviour) and total (internalising, externalising, sleep and other) problem scales. Higher
25 scores indicate increased emotional and behavioural problems. Total scores are classified into
26 a normal range (<83rd centile, T <60), borderline range (83rd-90th centile, T 60-63), and
27 clinical range (>90th centile, T ≥64).³⁵ The CBCL is known to have high reliability, validity
28 and cross-informant agreement for measuring children's emotional and behavioural
29 problems.³⁵
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41 *ASD traits* were assessed using the Quantitative Checklist for Autism in Toddlers (Q-CHAT).
42 The Q-CHAT is a parent-completed 25-item questionnaire, in which the child's behaviour is
43 scored on a 5-point (0-4) frequency scale. Higher total scores correspond to a higher
44 frequency of autistic traits. The Q-CHAT shows good test-retest reliability, face validity and
45 specificity, yet poor positive predictive value.^{36,37}
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51 *Cognitive assessment* was performed using the Bayley Scales of Infant and Toddler
52 Development – Third Edition (Bayley-III). The Bayley-III provides scores for a child's
53 overall cognitive, language and motor development. The cognitive standardised composite
54 score was used in this study; scores between 70-84 indicate mild cognitive impairment,
55 scores between 55-69 indicate moderate impairment, and scores lower than 55 indicate severe
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3 impairment³⁸. Reliability and validity of the Bayley-III have been shown to be robust,³⁹
4 although some studies report its underestimation of developmental problems.⁴⁰
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8 Assessments were carried out by staff experienced in the neurocognitive assessments of
9 toddlers.
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13 Analysis

14 Descriptive statistics and one-way ANOVA tests were performed in IBM SPSS Statistics for
15 Windows v.25. All other analyses were carried out in Stata v.16.
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20 Multiple imputation (MI) was carried out to account for missing data in CBCL (11/509,
21 2.24%), Q-CHAT (9/509, 1.8%), maternal EPDS (73/509, 14.3%), maternal BMI (27/509,
22 5.3%) and IMD rank (3/509, 0.6%). Variables were imputed simultaneously using the ‘mi
23 impute chained’ procedure that performs imputation by chained equations. The imputation
24 models had the same structural form as the analysis models, and included all variables that
25 appear in the corresponding analysis models (maternal EPDS, maternal BMI, multiple
26 pregnancy, parity, IMD rank, gestational age at birth, birthweight, sex, corrected age at
27 assessment, and Bayley III Cognitive Composite score); in addition, maternal age was also
28 included in the imputation model, as this predicted the incomplete variable and the
29 probability of a value being observed.⁴¹ To assess whether maternal age was predicting the
30 probability of a value being observed, we firstly constructed binary indicators, one for each
31 incomplete variable, that denoted whether the incomplete variable was missing their value
32 (coded 0) or not (coded 1). These indicators then formed the dependent variable in logistic
33 regression models that used maternal age as the independent variable. We used a 5% level to
34 define a significant association.
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48 Maternal EPDS and CBCL were imputed using Poisson regression; Q-CHAT, maternal BMI,
49 and the IMD rank were imputed using linear regression. 40 MI datasets were created. To
50 assess the stability of our MI parameters, we extracted the Monte Carlo error of each
51 parameter estimate and examined whether the error for the coefficient was less than 10% of
52 the parameter’s standard error estimate. MI estimates were used for the primary analyses and
53 compared to the estimates from complete-case (CC, individuals who had no missing data pre-
54 imputation) analyses. Normal probability plots of residuals from the CC analyses were
55 examined.
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5 The analysis models were multiple linear regressions fitted using the ‘mi estimate’ procedure,
6 which estimates effects after application of Rubin’s rules.⁴² To account for the small amount
7 of clustering in our data (twin/triplet siblings), the models’ standard errors were obtained
8 using Stata’s robust cluster estimator ‘vce(cluster *idvar*)’. For continuous variables, Cohen’s
9 f-squared effect sizes were calculated using $f^2 = (R_{AB}^2 - R_A^2)/(1 - R_{AB}^2)$, where R_{AB}^2 is the R-
10 squared value from a regression model that includes the variable of interest as well as all the
11 covariates used in the model, and R_A^2 is the R-squared value from the regression model that
12 includes only the covariates.^{43,44} For binary variables, Cohen’s f-squared effect sizes were
13 produced after estimating first the Cohen’s d using the formula: $f^2 = \frac{d}{2k}$, where k is the
14 number of groups. As a measure of dispersion, Cohen’s d used the average root mean-square
15 error over the MI datasets. Adjusted R-squared values after MI were extracted after
16 estimating the model with the user-written ‘mibeta’ command with the ‘fisherz’ option,⁴⁵
17 which calculates R-squared measures for linear regression with MI data. The significance of
18 the joint effect of the categorical variable parity was assessed using ‘mi test’ which performs
19 Wald tests of composite linear hypotheses.
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34 *Primary outcome measures* were children’s total CBCL raw score and Q-CHAT score.

35 *Secondary outcome measures* were CBCL internalising and externalising scores. The effect
36 of maternal EPDS score was adjusted for IMD rank, maternal age, maternal BMI, maternal
37 parity, pregnancy size, and the following child’s variables: continuous gestational age, birth
38 weight, Bayley-III cognitive composite score, and corrected age at assessment. The
39 interaction between preterm birth and maternal depressive symptoms was explored using a
40 complete case analysis in both CBCL and Q-CHAT models, using a dichotomised measure of
41 gestational age. EPDS, CBCL and Q-CHAT scores were compared between term (≥ 37 weeks
42 gestation) and preterm infants (< 37 weeks gestation) using the complete case dataset.
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51 In order to investigate the specificity of the association between maternal EPDS scores and
52 child’s behavioural outcomes (versus cognitive outcomes) we repeated the analyses to predict
53 Bayley-III Cognitive Composite score, with the following variables: IMD rank, maternal age,
54 maternal BMI, maternal parity, pregnancy size, and the following child’s variables:
55 gestational age, birth weight, corrected age at assessment, and Q-CHAT score. CBCL score
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3 was not included in the model predicting cognitive outcome, because cognition was not a
4 significant predictor of CBCL (see Results).
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8 As all mothers had their EPDS score measured near term (or term-corrected in the case of
9 mothers of preterm infants), we further investigated the association between time elapsing
10 between baby's birth and mother's EPDS assessment and EPDS score, in order to avoid
11 erroneously identifying 'baby blues' in mothers of term-born infants versus postnatal
12 depression in mothers of preterm infants. This post-hoc analysis was performed using
13 Poisson regression.
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20 Patient and Public Involvement

21 The current study was developed in consultation with the Weston Programme for Family
22 Centered Research, which involves parents to define what research is valuable to them, and to
23 allow them to lead it with support from the scientists in the Centre for the Developing Brain.
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29 Results

30 Descriptive statistics

31 Our sample of 509 toddlers were followed up at a median corrected age of 18.4 months
32 (range 17.3 – 24.3 months). 51 (10.0%) of these were twins, and 3 (0.59%) were triplets. Of
33 the 509, 21 (4.13%) mothers scored above a clinical cut-off (≥ 13) on the EPDS;(26) the
34 distribution of maternal EPDS scores is shown graphically in Supplementary Figure 1.
35 Demographic data are shown in Table 1. Complete data were available for 400 (78.6%)
36 participants. Missing data were imputed and thus all 509 subjects were included in the
37 primary and secondary analyses. One participant was excluded from the cognition analysis
38 after examining the quintiles of the residuals against the theoretical quintiles of a normal
39 distribution. The mean CBCL T score was 46.9 (SD 9.5) (Table 1); using CBCL-specified
40 cut-offs,³⁵ 449 (90.2%) of participants had a CBCL score in the normal range, 30 (6.0%)
41 were borderline, and 19 (3.8%) scored in the clinical range. The mean Q-CHAT score was
42 30.5 (SD 9.3) (Table 1). The mean Bayley III Cognitive Composite score in our sample was
43 100 (SD 11.4) (Table 1), which corresponds to the standardised test mean;³⁸ 480 (94.3%) of
44 participants had a normal cognitive score, 24 (4.7%) had mild impairment, 5 (1%) had
45 moderate impairment, and nil had severe impairment. This distribution is not dissimilar from
46 that of the normative sample.³⁸
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Association between maternal EPDS score and toddler CBCL and Q-CHAT scores

Predictors of children's CBCL and Q-CHAT scores after multiple imputation are shown in Table 2. Higher maternal EPDS score was associated with children's higher CBCL Total score ($B=0.93$, 95% CI 0.43-1.44, $p<0.001$, $f^2=0.05$) and Q-CHAT score ($B=0.27$, 95% CI 0.03-0.52, $p=.031$, $f^2=0.01$) (Table 2). These associations are presented graphically in Figure 1 and Figure 2, respectively. Boys had higher CBCL and Q-CHAT scores than girls. Higher Q-CHAT scores were associated with lower IMD rank (i.e., greater socio-economic deprivation) and lower Bayley-III cognitive composite scores. Parity was not a significant predictor of outcome in any of the models (Table 2).

Association between maternal EPDS score and toddler CBCL internalising and externalising scores

Higher maternal EPDS score was associated with both internalising ($B=0.22$, 95% CI 0.08-0.36, $p<0.01$, $f^2=0.03$) and externalising ($B=0.40$, 95% CI 0.20-0.61, $p<0.001$, $f^2=0.05$) symptoms in children (Supplementary Table 1 and 2, respectively). Comparison of the imputed model analyses to the complete-case analyses showed that results were consistent for the CBCL model (Supplementary Table 3). Comparison for the Q-CHAT model showed that maternal EPDS was a significant predictor in the imputed model, but not in the complete-case analysis (Supplementary Table 3).

Interaction effect of preterm birth and maternal EPDS score on toddler CBCL and Q-CHAT scores

Maternal EPDS scores did not differ between preterm and term groups in the complete dataset ($t(434)=0.11$, $p=0.92$). CBCL scores ($t(496)=0.95$, $p=0.34$) and Q-CHAT scores ($t(122.6)=0.50$, $p=0.62$) did not differ between preterm and term groups in the complete dataset. Maternal EPDS score did not disproportionately affect preterm children with respect to CBCL or Q-CHAT scores (Table 3).

Association between maternal EPDS score and toddler cognitive outcomes

Predictors of children's cognitive score are shown in Table 4. Maternal EPDS score at term was not associated with toddlers' cognitive outcomes ($B=-0.22$, 95% CI -0.50-0.05, $p=.108$).

Effect of time-lag between baby's birth and mother's EPDS assessment and EPDS score

Mothers who gave birth prematurely (<37 weeks gestation) had their EPDS score assessed on average 7.7 weeks later post-delivery than mothers who gave birth at term (preterm

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3 participants $M=8.9$ (SD 4.8), term participants $M=1.2$ (SD 1.3); $t(99.4)=15.5$, $p<.001$). The
4 time-lag between birth and EPDS assessment did not predict maternal EPDS score, and there
5 was no evidence of a significant interaction between gestation and birth-to-assessment time-
6 lag (Supplementary Table 4 and 5, respectively).
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10 11 **Discussion**

12 **Principal findings**

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14 Our results showed that more maternal self-reported depressive symptoms shortly after birth
15 were associated with greater parent-reported toddlers' behavioural problems – both
16 internalising and externalising symptoms – and ASD traits, but not with cognitive outcomes.
17 Given that fewer than 5% of the mothers in our cohort had EPDS scores above a clinical
18 threshold,³³ our findings indicate that even subclinical depressive symptoms – i.e. not only
19 diagnostic postnatal depression – adversely impact children's behavioural outcomes. In
20 addition, our cohort was typically developing with few CBCL scores reaching a concerning
21 threshold; our results could be interpreted within the conceptual framework of mental illness
22 lying on a continuum with typical behavioural traits.⁴⁶ Our findings further showed that
23 preterm birth did not influence the association between self-reported maternal depressive
24 symptoms and parent-reported infants' behavioural outcomes in toddlerhood. This indicates
25 that in this context preterm birth may not be regarded as a vulnerability or plasticity factor.
26 Interestingly, mothers of preterm infants did not report more depressive symptoms compared
27 to mothers of term infants in this study.
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41 **Comparison to prior literature**

42 Our results with respect to internalising and externalising symptoms are in line with previous
43 studies, including large population cohort studies, that showed an association between
44 postnatal maternal depression and young children's emotional and behavioural problems.¹¹
45 Another previous study in 18-month old toddlers found that maternal depression was
46 associated with internalising and dysregulated behaviour, but not externalising symptoms.⁴⁷
47 This difference between our and Conroy et al.'s findings may have arisen from their
48 exclusion of infants born <36 weeks and their use of a clinical diagnosis of depression for
49 mothers, rather than the continuous self-reported approach we employed. Interestingly, our
50 finding that even subclinical depressive symptoms may adversely impact parent-reported
51 child behavioural outcomes is in line with recent data showing that low- as well as high-level
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3 depressive symptoms are associated with internalising and externalising symptoms in
4 children aged 3 years.⁴⁸
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8 The results showing an association between maternal postnatal depressive symptoms and
9 parental report of childhood ASD traits are less robust and need to be interpreted with
10 caution. Although some prior studies have shown an association between antenatal maternal
11 depression and offspring's ASD,^{10,49} and postnatal depression has been suggested as a
12 potential focus of cross-domain studies of ASD,⁵⁰ there is no clear aetiological role of
13 maternal postnatal depression in the development of ASD *per se*. Also, given that mothers
14 with ASD are more likely to suffer from perinatal depression than mothers without ASD,⁵¹
15 and ASD is highly heritable,⁵² maternal depression may actually be a confounding rather than
16 causative factor in our observed results.
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26 The finding that preterm infants were not disproportionately affected by maternal depressive
27 symptoms supports Hadfield et al.'s findings that maternal distress at 9 months did not
28 differentially impact very preterm (<34 weeks) or late preterm (34-36⁺⁶ weeks) infants with
29 respect to socioemotional outcomes, although paternal distress did have an impact on very
30 preterm infants' outcomes.²⁴ However, our results differ from Gueron-Sela et al.'s finding
31 that very preterm (28-33 weeks) 12 month old infants' social outcomes were more influenced
32 by maternal emotional distress at 6 months than term infants' outcomes.²² The inconsistent
33 findings may be due to methodological differences: for instance, our infant assessment being
34 conducted at 18 months corrected age when social competency is more developed, our
35 assessment of maternal depressive symptoms being in the very early postnatal period, or our
36 use of a screening measure, the Q-CHAT, as a measure of ASD traits. Importantly, the lack
37 of support for a diathesis-stress or differential susceptibility model of maternal mental state
38 on preterm infants in our study must be viewed in the context of our results also showing no
39 difference in CBCL and Q-CHAT scores between term and preterm infants. This is in
40 contrast to the existing literature that preterm infants are more likely than term infants to
41 develop behavioural problems, such as ADHD, in childhood and adolescence.^{19,30} It is
42 possible that the phenotypes of neurodevelopmental and neuropsychiatric disorders assessed
43 with the chosen behavioural measures may not be sufficiently expressed at 18 months
44 corrected age.⁵³ In addition, as briefly discussed above, much of the existing literature
45 emphasises the risk of extreme (<28 weeks) or very preterm (28-33 weeks) birth on later
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3 behavioural outcomes,^{19,30} whereas only 3.5% and 5.5% of our participants fell within the
4 extreme and very preterm group, respectively, and we thus may not have the power to show
5 any subtle effects.
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10 **Strengths & limitations of the study**

11 The strengths of this study lie primarily in its large sample and prospective data collection.
12 Moreover, the use of multiple imputation methodology has facilitated retention of a complete
13 dataset, thus minimising non-response bias and increasing parameter precision. A strength in
14 comparison to prior population cohort studies is that we assessed very early maternal
15 depressive symptoms, and our sample is perhaps more representative of today's society –
16 with increasing maternal age – than large cohort studies conducted in the 1990s-2000s. Given
17 the complex interplay of biological and environmental factors in the aetiology of behavioural
18 disorders, the inclusion of a substantive proportion of preterm infants in our cohort also offers
19 an important insight into the role of preterm birth in behavioural outcomes; moreover, our
20 results represent the full gestational spectrum, rather than discrete gestational categories. In
21 addition, using maternal depressive symptoms as a continuous, rather than dichotomous,
22 variable allows a more nuanced understanding of the role maternal postnatal depressive
23 symptoms may play in influencing children's outcomes.
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36 There are several limitations to this study that necessitate our findings to be considered with
37 caution. Firstly, differences in birth-to-EPDS-assessment time-lags are a potential
38 confounder, given the time-sensitive nature of early-onset temporary baby blues and later-
39 onset pathological postnatal depression. Mothers of infants born at term were assessed early
40 post-delivery, within the period one would anticipate baby blues to present, whereas mothers
41 of preterm participants were on average assessed later, when postnatal depression
42 predominates.^{1,54} Although our post-hoc analyses showed that the time elapsed from birth to
43 EPDS assessment was not associated with maternal EPDS score, providing reassurance that
44 our assessments of mothers of term-born infants were not inflated by the common temporary
45 symptoms of baby blues, it is possible that we did not capture the full extent of later-onset
46 depressive symptoms in mothers of term-born infants. This may explain why maternal EPDS
47 scores did not differ between preterm and term groups in our complete dataset analysis,
48 contrary to the current literature,²⁸ as well as why our rate of postpartum depression, using an
49 EPDS cut-off of 13, was low (4.1%) compared to the previously documented UK community
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3 prevalence rate of 8.9% at eight weeks postpartum.⁵⁵ Our results must therefore be
4 interpreted with some caution.
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9 Secondly, although statistical techniques were used to impute missing data and mitigate this
10 problem, 14.3% of maternal EPDS scores were missing. This rate of missingness may relate
11 to some mothers being reluctant to complete a questionnaire at the time their child is having
12 an MRI, or due to simultaneous childcare duties. Thirdly, a number of important confounders
13 that are likely to affect children's behavioural outcomes were not assessed in this study,
14 including genetic risk for psychiatric disorders,⁵⁶ parental psychiatric co-morbidities,⁴⁷
15 chronicity of postnatal depressive symptoms,⁴⁸ antenatal maternal depression, paternal
16 depression and subsequent parent-infant attachment, and inter-parental conflict.¹¹ Thus, we
17 are unable to conclude whether our observed associations between early postnatal maternal
18 depressive symptoms and children's behavioural outcomes are moderated or mediated by
19 other parental and/or psychiatric factors.
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29 Fourthly, whilst our study included a reasonable proportion of preterm infants (97/509, 19%),
30 our sample was not random, as preterm children were selectively recruited for the DHCP;
31 indeed, preterm infants are over-represented in our sample when compared to the UK
32 population incidence (7.3%),⁵⁷ which may limit the study's generalisability to the general
33 population. This over-representation of preterm infants may explain why our mean maternal
34 age is higher than the national mean age of 30.7,⁵⁸ given that increasing maternal age is
35 associated with increased risk of adverse pregnancy outcomes.⁵⁹ Furthermore, although a
36 19% prevalence of preterm birth is high for a community sample, the proportion of very and
37 extreme preterm infants in our sample is small, and this may not have provided sufficient
38 power to detect any differential susceptibility effect of preterm birth on outcomes.
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48 Sixthly, the effect sizes of the association between maternal EPDS score and behavioural
49 problems and ASD traits, respectively, were small; this raises questions regarding the clinical
50 significance of our findings and potentially explains some of the inconsistency between this
51 and previous studies. Even within our analyses, the association between maternal depressive
52 symptoms and ASD traits was not observed in our complete case analysis, thus calling into
53 question the validity of this result. It is also important to highlight the continuum of ASD
54 traits that are conceptualised by the Q-CHAT,³⁶ as well as its poor positive predictive value;³⁷
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3 the presence of traits does not imply a diagnosis of ASD, and this distinction may also
4 explain the contrast to previous studies.
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8 Finally, it is well documented that maternal depression influences reporting of ASD traits,⁶⁰
9 Q-CHAT,⁶¹ and CBCL scores.⁶² Our study used maternal report of maternal depressive
10 symptoms, and our outcome measures were parent-completed questionnaires; despite the
11 CBCL showing good cross-informant agreement,³⁵ it is thus possible that reporting bias with
12 common method variance could have skewed our results.
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18 **Implications of our findings**

19 Of greatest importance to clinicians and policymakers is our finding that even *subclinical*
20 self-reported maternal depressive symptoms are associated with parent-reported behavioural
21 outcomes of offspring. This has significant implications for the risk-stratification of women
22 and their babies in the postnatal period, during which contact with medical professionals is
23 already established. Identifying high risk families and providing appropriate supportive
24 measures at the early postnatal stage may help to prevent future psychiatric morbidity.
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32 **Future research**

33 Further follow-up of large cohorts of preterm and term infants, to an age when behavioural
34 phenotypes may become more pronounced, is needed to investigate whether the long-term
35 developmental trajectories of term and ex-preterm infants are differentially susceptible to
36 changes of postnatal maternal mental health. Future research should consider both maternal
37 and paternal mental health, as well as socioeconomic and environmental factors on child
38 outcomes. Such follow-up should use independent, objective assessments of child
39 behavioural outcomes in order to avoid the common method variance inherent to parent-
40 reported measures. In addition, further study is also needed to elucidate the role of maternal
41 depression in the aetiology of ASD, controlling for both diagnostic and sub-clinical maternal
42 ASD symptomatology. Finally, it is crucial for future research to elucidate the interplay of
43 biochemical and neurodevelopmental changes that may mediate and confound the translation
44 of environmental exposures into distal behavioural phenotypes.
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56 **Conclusion**

57 This prospective longitudinal cohort study found no evidence to support the concept of
58 preterm birth as a vulnerability or plasticity factor with respect to the effect of maternal
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3 depressive symptoms on behavioural development. However, we showed that early
4 subclinical maternal postnatal depressive symptoms were associated with behavioural
5 problems in children on parent-reported measures. This adds to the increasing body of
6 literature indicating the role of subclinical and early postnatal depressive symptoms in the
7 aetiology of childhood behavioural disorders. These findings are of great relevance to child
8 and public health, and further research may strengthen its implications for developing
9 strategies to facilitate effective screening and support for women and children, enabling all to
10 reach their full potential.
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32 **Investigation:** SF, AC; **Data curation:** IK, AL; **Formal analysis:** IK, GV, AP, CN;

33 **Writing – original draft preparation:** IK; **Writing – Review & Editing:** GV, AL, SF, AC,
34 SC, AP, ADE, CN; **Visualisation:** IK, GV; **Funding acquisition:** SC, ADE; **Supervision:**
35 AP, ADE, CN.
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Table 1: Socio-demographic, maternal and clinical characteristics (n=509)

Variable	Number (%) [*]
Sex: Male	274 (53.8)
Index of Multiple Deprivation (IMD) quintiles	
1 (least deprived) ^a	65 (12.8)
2	87 (17.2)
3	108 (21.3)
4	173 (34.2)
5 (most deprived)	73 (14.4)
Gestational age at birth (weeks), median [range]	39.7 [20 – 43]
Gestational category	
Extremely preterm (<28 weeks)	18 (3.5)
Very preterm (28-32 weeks)	28 (5.5)
Late preterm (32-37 weeks)	51 (10.0)
Term (≥37 weeks)	412 (80.9)
Birthweight (g), median [range]	3290 [450 – 4750]
Multiple pregnancy	54 (10.6)
Maternal parity	
0	332 (65.2)
1	124 (24.4)
2	32 (6.3)
3+	21 (4.2)
Maternal BMI (kg/m ²), median [range]	23.2 [15.3 – 43.6]
Maternal age at infant's birth (years), mean (SD) [range]	34.2 (4.8) [17 – 52]
Maternal ethnicity	
White	272 (53.4)
Black/Black British	56 (11.0)
Asian/Asian British	28 (5.5)
Chinese	18 (3.5)
Mixed – White & Asian	4 (0.8)
Mixed – White & Black	4 (0.8)
Any other	30 (5.9)
Do not wish to answer	9 (1.8)
No data	88 (17.3)
Bayley III cognitive composite score, mean (SD) [range]	100 (11.4) [55 – 125]
CBCL total T score, mean (SD) [range]	46.9 (9.5) [28 – 69]
Q-CHAT total score, mean (SD) [range]	30.5 (9.3) [8 – 70]
EPDS score, median [range]	4 [0 – 28]
EPDS score, n (%)	
<13	415 (8.2)
≥13	21 (4.1)
No data	73 (14.3)

^a Quintile 1 corresponds to the highest, least deprived, IMD rankings.

* unless otherwise specified

Table 2: CBCL and Q-CHAT model predictors using multiple imputation without interaction. (Cf. Supplementary Table 3 for complete case analysis)

	CBCL			Q-CHAT		
	B [95%CI]	p	f ²	B [95%CI]	p	f ²
Maternal EPDS	0.93 [0.43, 1.44]	<.001 ***	0.05	0.27 [0.03, 0.52]	.031 *	0.01
Maternal BMI	-0.09 [-0.44, 0.26]	.621	-	0.06 [-0.13, 0.24]	.538	-
Multiple pregnancy	3.15 [-3.07, 9.37]	.320	-	1.33 [-2.62, 5.28]	.509	-
Parity						
1	-2.52 [-5.96, 0.93]	.151	-	-2.14 [-4.02, -0.27]	.025 ^a	-
2	-3.23 [-9.16, 2.70]	.285	-	0.88 [-1.99, 3.75]	.548	-
3+	-1.37 [-8.36, 5.61]	.699	-	-0.49 [-4.57, 3.60]	.815	-
IMD rank	-1.48 [-3.33, 0.37]	.117	-	-1.50 [-2.60, -0.40]	.008 **	0.02
Gestational age at birth (weeks)	0.10 [-0.65, 0.85]	.786	-	0.26 [-0.17, 0.70]	.233	-
Birthweight (kg)	0.56 [-2.65, 3.78]	.731	-	-1.24 [-2.93, 0.46]	.151	-
Sex:female	-4.14 [-6.96, -1.31]	.004 **	0.06	-1.95 [-3.42, -0.48]	.009 **	0.05
Corrected age at assessment (months)	-0.90 [-2.17, 0.37]	.166	-	-0.16 [-0.91, 0.59]	.677	-
Cognition	-0.05 [-0.20, 0.09]	.467	-	-0.27 [-0.35, -0.20]	<.001 ***	0.12

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL model adjusted R² = 0.0676. Q-CHAT model adjusted R² = 0.193.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

^a Wald test of whole parity variable in Q-CHAT model: F(3, 476.9) = 1.88, p = .133

Effect size (Cohen’s f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.⁴³

- indicates data not given, as predictor not significant to 0.05.

Table 3: CBCL and Q-CHAT model predictors using complete case analysis with interaction of ‘EPDS x term’.

	CBCL		Q-CHAT	
	B [95%CI]	p	B [95%CI]	p
Maternal EPDS	0.89 [-0.24, 2.02]	.121	0.24 [-0.28, 0.75]	.365
Maternal BMI	-0.01 [-0.39, 0.37]	.955	0.00 [-0.16, 0.17]	.982
Multiple pregnancy	1.76 [-6.65, 10.17]	.681	0.97 [-2.07, 4.01]	.532
Parity				
1	-2.75 [-6.49, 0.99]	.149	-1.42 [-3.30, 0.46]	.139
2	-3.49 [-10.36, 3.37]	.317	0.16 [-2.84, 3.16]	.917
3+	-1.17 [-9.69, 7.35]	.788	-1.13 [-4.24, 1.98]	.476
IMD rank	-1.41 [-3.54, 0.73]	.195	-1.68 [-2.64, -0.72]	.001 **
Gestation: term	1.25 [-8.34, 10.85]	.797	2.64 [-1.74, 7.02]	.236
Birthweight (kg)	-1.01 [-4.08, 2.05]	.516	-2.25 [-3.73, -0.78]	.003 **
Sex: female	-4.64 [-7.83, -1.44]	.005 **	-2.22 [-3.72, -0.71]	.004 **
Corrected age at assessment (months)	-0.83 [-2.27, 0.62]	.261	-0.39 [-1.18, 0.04]	.335
Cognition	-0.03 [-0.20, 0.14]	.720	-0.22 [-0.29, -0.15]	<.001 ***
EPDS x gestation:term	-0.01 [-1.30, 1.28]	.991	-0.02 [-0.60, 0.56]	.950

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL model adjusted R² = 0.0865. Q-CHAT model adjusted R² = 0.215.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Gestation: term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth.

Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months. EPDS x gestation:term = interaction term between maternal EPDS score and term gestation at birth.

Table 4: Cognition model predictors using multiple imputation.

	B [95%CI]	p
Maternal EPDS	-0.22 [-0.50, 0.05]	.108
Maternal BMI	-0.32 [-0.52, -0.13]	.001 **
Multiple pregnancy	1.65 [-2.49, 5.79]	.433
Parity		
1	-0.46 [-2.67, 1.76]	.686
2	-3.47 [-6.69, -0.25]	.035 ^a
3+	-4.57 [-9.53, 0.40]	.072
IMD rank	1.43 [0.37, 2.50]	.009 **
Gestational age at birth (weeks)	0.45 [-0.07, 0.96]	.091
Birthweight (kg)	0.81 [-1.24, 2.87]	.436
Sex: female	1.99 [0.24, 3.74]	.026 *
Corrected age at assessment (months)	-0.75 [-1.59, 0.08]	.075
Q-CHAT score	-0.39 [-0.50, -0.28]	<.001 ***

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.231

B = unstandardised coefficient.

Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age.

Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months. Q-CHAT score = infant's Q-CHAT score at 18 month assessment.

^a Wald test of whole parity variable in cognition model: F(3, 482.9)=2.41, p=0.067

Fig.1 Children's predicted CBCL scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age.

Fig.2 Children's predicted Q-CHAT scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age.

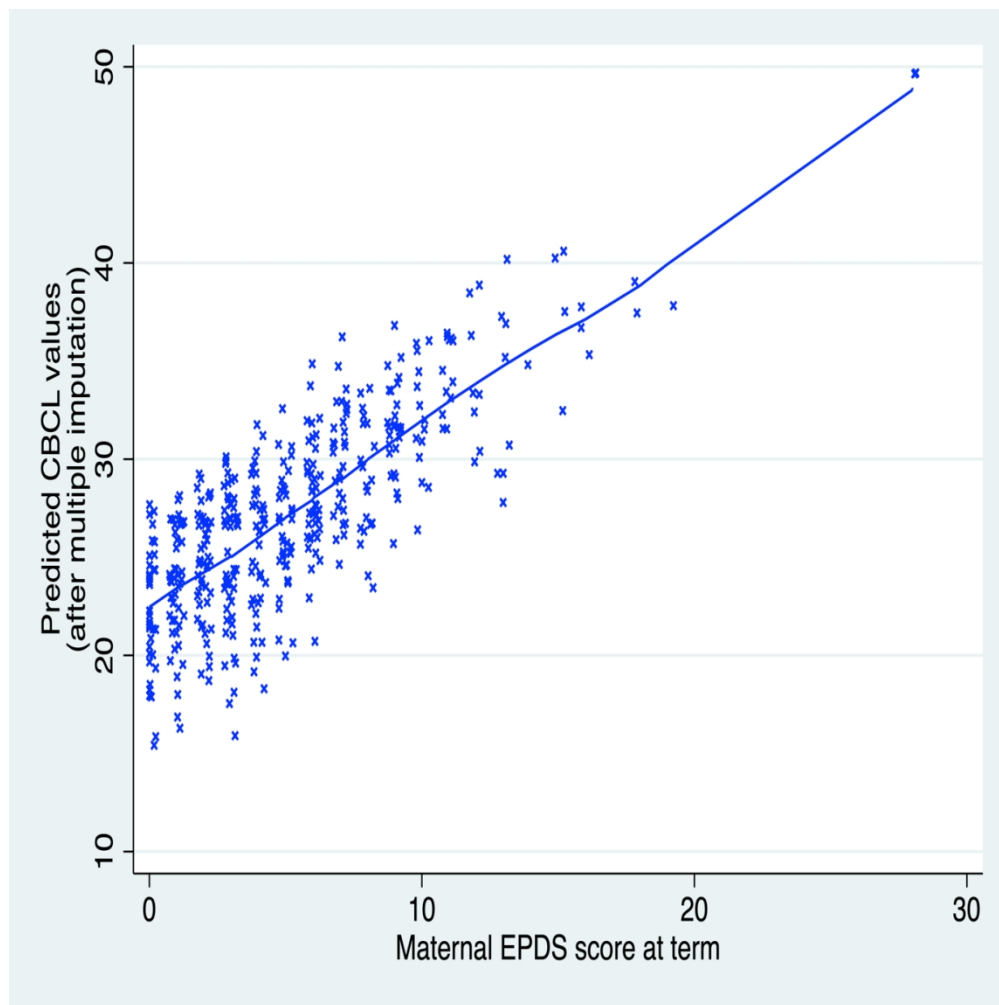


Fig.1 Children’s predicted CBCL scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age

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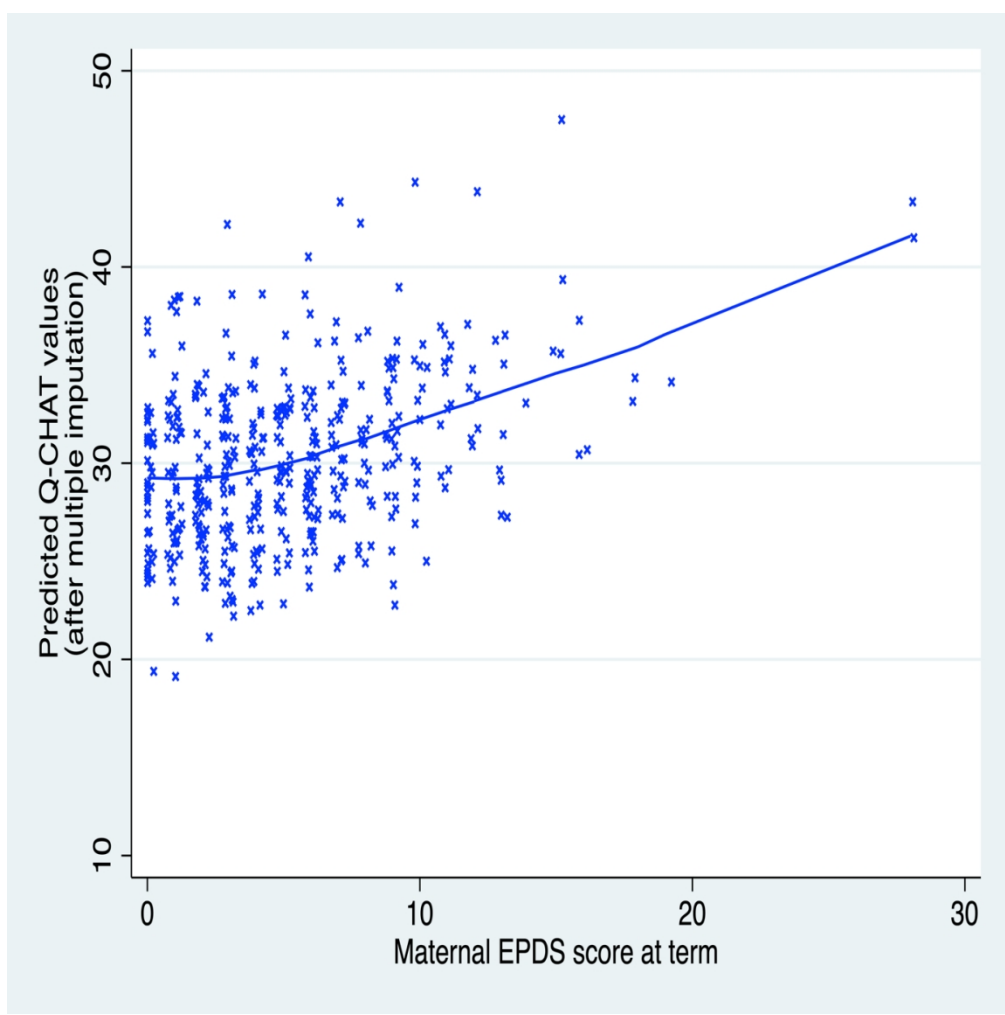


Fig.2 Children’s predicted Q-CHAT scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age.

158x158mm (220 x 220 DPI)

Supplemental material

Supplementary Table 1: CBCL internalising symptom model predictors using multiple imputation.

Supplementary Table 2: CBCL externalising symptom model predictors using multiple imputation.

Supplementary Table 3: CBCL and Q-CHAT model predictors using complete case analysis without interaction.

Supplementary Table 4: EPDS score predictors.

Supplementary Table 5: EPDS score predictors including interaction 'term x time-lag'.

Supplementary Figure 1: Histogram showing the distribution of maternal EPDS scores at term-equivalent age.

Supplementary Table 1: CBCL internalising symptom model predictors using multiple imputation.

	B [95%CI]	p	f²
Maternal EPDS	0.22 [0.08, 0.36]	.003 **	0.03
Maternal BMI	-0.04 [-0.13, 0.06]	.436	-
Multiple pregnancy	0.58 [-1.10, 2.27]	.497	-
Parity			
1	-0.37 [-1.41, 0.67]	.487	-
2	-1.33 [-3.09, 0.42]	.136	-
3+	0.64 [-1.34, 2.62]	.524	-
IMD rank	-0.41 [-0.91, 0.10]	.115	-
Gestational age at birth (weeks)	0.22 [-0.00, 0.44]	.053	-
Birthweight (kg)	-0.97 [-1.90, -0.05]	.038 *	0.005
Sex: female	-0.51 [-1.35, 0.33]	.232	-
Corrected age at assessment (months)	0.02 [-0.41, 0.45]	.923	-
Cognition	-0.05 [-0.10, -0.01]	.016 *	0.01

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.0566.

B = unstandardised coefficient.

Outcome variable = Child Behaviour Checklist internalising sub-score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.¹

- indicates data not given, as predictor not significant to 0.05.

Supplementary Table 2: CBCL externalising symptom model predictors using multiple imputation.

	B [95%CI]	p	f²
Maternal EPDS	0.40 [0.20, 0.61]	<.001 ***	0.05
Maternal BMI	0.01 [-0.17, 0.15]	.933	-
Multiple pregnancy	2.51 [-0.29, 5.31]	.079	-
Parity			
1	-1.06 [-2.53, 0.42]	.160	-
2	-0.61 [-3.55, 2.33]	.682	-
3+	-0.96 [-4.47, 2.56]	.593	-
IMD rank	-0.24 [-1.11, 0.63]	.585	-
Gestational age at birth (weeks)	-0.07 [-0.40, 0.27]	.701	-
Birthweight (kg)	1.03 [-0.38, 2.44]	.153	-
Sex: female	-1.80 [-3.07, -0.53]	.006 **	0.06
Corrected age at assessment (months)	-0.40 [-0.95, 0.16]	.161	-
Cognition	0.03 [-0.03, 0.10]	.322	-

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.0612.

B = unstandardised coefficient.

Outcome variable = Child Behaviour Checklist externalising sub-score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal

Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age.

Cognition = infant Bayley III score at 18 months.

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.¹

- indicates data not given, as predictor not significant to 0.05.

Supplementary Table 3: CBCL and Q-CHAT model predictors using complete case analysis without interaction.

	CBCL		Q-CHAT	
	B [95%CI]	p	B [95%CI]	p
Maternal EPDS	0.88 [0.35, 1.41]	.001 **	0.21 [-0.02, 0.44]	.069
Maternal BMI	-0.01 [-0.38, 0.37]	.963	0.01 [-0.16, 0.17]	.930
Multiple pregnancy	1.50 [-6.87, 9.87]	.724	0.43 [-2.50, 3.37]	.772
Parity				
1	-2.83 [-6.60, 0.94]	.141	-1.54 [-3.41, 0.34]	.108
2	-3.49 [-10.3, 3.35]	.316	0.13 [-2.85, 3.10]	.933
3+	-1.38 [-10.0, 7.30]	.755	-1.43 [-4.50, 1.64]	.360
IMD rank	-1.44 [-3.56, 0.67]	.181	-1.75 [-2.70, -0.79]	<.001 ***
Gestational age at birth (weeks)	0.01 [-0.90, 0.91]	.987	0.10 [-0.33, 0.54]	.639
Birthweight (kg)	-0.65 [-4.38, 3.08]	.733	-1.81 [-3.63, 0.00]	.050
Sex: female	-4.57 [-7.82, -1.31]	.006 **	-2.12 [-3.60, -0.64]	.005 **
Corrected age at assessment (months)	-0.84 [-2.26, 0.59]	.247	-0.41 [-1.18, 0.35]	.290
Cognition	-0.03 [-0.20, 0.13]	.689	-0.23 [-0.30, -0.15]	<.001 ***

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL adjusted R² = 0.0862. Q-CHAT adjusted R² = 0.2103.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist externalising sub-score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Gestation (weeks) = dummy variable: 34-36+6 weeks and ≥37 weeks gestation at birth. Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Supplementary Table 4: EPDS score predictors.

	IRR [95%CI]	p
Time-lag (weeks)	1.01 [0.97, 1.05]	.647
Gestation:term	0.91 [0.64, 1.31]	.627
IMD rank	1.00 [1.00, 1.00]	.103
Multiple pregnancy	0.66 [0.46, 0.96]	.031 *
Parity		
1	0.79 [0.66, 0.95]	.011 *
2	0.87 [0.60, 1.28]	.491
3+	0.84 [0.54, 1.31]	.445
Birthweight (kg)	0.98 [0.83, 1.17]	.847
Sex:female	1.13 [0.98, 1.31]	.098

p<0.05 *; p<0.01 **; p<0.001 ***

Pseudo R² = 0.0228

IRR = incidence rate ratio

Outcome variable = maternal Edinburgh Postnatal Depression Scale (EPDS) score at term-equivalent age. Time-lag (weeks) = time in weeks between birth and EPDS assessment. Gestation:term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren).

Supplementary Table 5: EPDS score predictors including interaction ‘term x time-lag’.

	IRR [95%CI]	p
Time-lag (weeks)	1.00 [0.97, 1.04]	.823
Gestation: term	0.88 [0.58, 1.34]	.553
IMD rank	1.00 [1.00, 1.00]	.104
Multiple pregnancy	0.66 [0.46, 0.96]	.029 *
Parity		
1	0.79 [0.66, 0.95]	.010 *
2	0.87 [0.60, 1.28]	.480
3+	0.85 [0.55, 1.31]	.458
Birthweight (kg)	0.97 [0.83, 1.15]	.756
Sex:female	1.13 [0.98, 1.30]	.100
Term x time-lag (weeks)	1.01 [0.94, 1.10]	.735

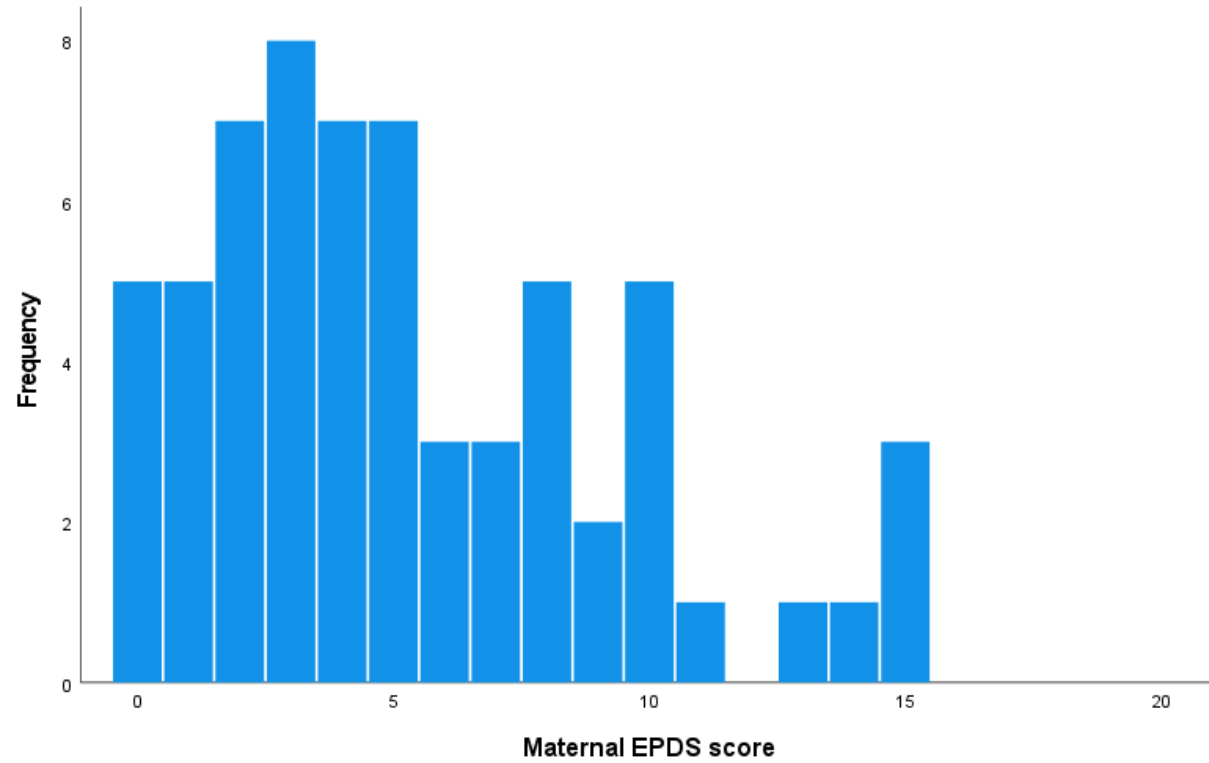
p<0.05 *; p<0.01 **; p<0.001 ***

Pseudo R² = 0.0230

IRR = incidence rate ratio

Outcome variable = maternal Edinburgh Postnatal Depression Scale (EPDS) score at term-equivalent age. Time-lag (weeks) = time in weeks between birth and EPDS assessment. Gestation: term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Term x time-lag (weeks): interaction term between term gestation at birth and time-lag between birth and maternal EPDS assessment.

Supplementary Figure 1: Histogram showing the distribution of maternal EPDS scores at term-equivalent age.



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3 **Supplemental reference list**
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- 5 1. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. L. Erlbaum Associates; 1988.
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For peer review only

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	1, 2
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	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
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
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
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, 8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	7
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
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
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)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11, 12

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, 12, 13
2			(b) Report category boundaries when continuous variables were categorized	
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, 12, 13
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12	Discussion			
13	Key results	18	Summarise key results with reference to study objectives	13
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	15- 17
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16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
18				
19				
20	Generalisability	21	Discuss the generalisability (external validity) of the study results	15- 17
21				
22	Other information			
23	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	3
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27 *Give information separately for exposed and unexposed groups.

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

Postnatal maternal depressive symptoms and behavioural outcomes in term- and preterm-born toddlers: a longitudinal UK community cohort study.

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Paediatrics
Keywords:	MENTAL HEALTH, Child & adolescent psychiatry < PSYCHIATRY, Developmental neurology & neurodisability < PAEDIATRICS, Depression & mood disorders < PSYCHIATRY, NEONATOLOGY

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1 **Postnatal maternal depressive symptoms and behavioural outcomes in term- and**
2 **preterm-born toddlers: a longitudinal UK community cohort study.**

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4 A^a (MD); Counsell SJ^a (PhD); Pickles, A^b (FMedSci); Edwards, AD^a (FMedSci); Nosarti, C^{a,d}
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1
2
3 35 **Abstract**

4 36 **Objectives:** To examine the association between maternal depressive symptoms in the
5 37 immediate postnatal period and offspring's behavioural outcomes in a large cohort of term-
6 38 and preterm-born toddlers.

7 39 **Design and Participants:** Data were drawn from the Developing Human Connectome
8 40 Project. Maternal postnatal depressive symptoms were assessed at term-equivalent age, and
9 41 children's outcomes were evaluated at a median corrected age of 18.4 months (range 17.3 –
10 42 24.3).

11 43 **Exposure and outcomes:** Preterm birth was defined as <37 weeks completed gestation.
12 44 Maternal depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale
13 45 (EPDS). Toddlers' outcome measures were parent-rated Child Behaviour Checklist 1^{1/2}-5
14 46 Total (CBCL) and Quantitative Checklist for Autism in Toddlers (Q-CHAT) scores.
15 47 Toddlers' cognition was assessed with the Bayley Scales of Infant and Toddler Development
16 48 – Third Edition (Bayley-III).

17 49 **Results:** Higher maternal EPDS scores were associated with toddlers' higher CBCL (B=0.93,
18 50 95% CI 0.43-1.44, p<0.001, f²=0.05) and Q-CHAT scores (B=0.27, 95% CI 0.03-0.52,
19 51 p=.031, f²=0.01). Maternal EPDS, toddlers' CBCL and Q-CHAT scores did not differ
20 52 between preterm (n=97; 19.1% of the total sample) and term participants. Maternal EPDS
21 53 score did not disproportionately affect preterm children with respect to CBCL or Q-CHAT
22 54 scores.

23 55 **Conclusions:** Our findings indicate that children whose mothers reported increased
24 56 depressive symptoms in the early postnatal period, including subclinical symptoms, exhibit
25 57 more parent-reported behavioural problems in toddlerhood. These associations were
26 58 independent of gestational age. Further research is needed to confirm the clinical significance
27 59 of these findings.
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Strengths and limitations of this study

- Prospective study with a large sample, using multiple imputation to reduce non-response bias.
- Maternal depressive symptoms assessed as a continuous variable, providing more nuanced information about the significance of subclinical symptoms.
- Maternal depressive symptoms assessed earlier than in previous studies, enabling recognition of early screening opportunities for families.
- Potential common method variance bias through parent-completed child behavioural assessments.
- Unknown paternal and parental factors, such as comorbid psychiatric conditions, that may confound our findings.

Keywords

Postpartum Depression; Child Development; Autism; Mental Health; Child Behavior; Mood Disorder; Preterm Birth.

Declarations

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2
3 102 **Conflict of interest / Competing interests**
4

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7

8 105 ADE received consulting fees from Chiesi Farmaceutici (advice on neuroprotection in
9 newborn infants) and Medtronic (unpaid participation in scientific advice committee). ADE
10 106
11 107 has a patent on Xenon as an organ protectant (No P023708WO). ADE was Chair of the Data
12 108
13 Monitoring and Ethics Committee for the Baby-Oscar Trial, and served on the Data
14 109
15 Monitoring and Ethics Committee for the PAEN Trial.
16

17 110

18
19 111 There are no other relationships or activities that could appear to have influenced the
20 112 submitted work.
21

22 113

23
24 114 **Availability of data and material**

25 115 Research data are available upon reasonable request.
26

27 116

28
29 117 **Code availability**

30 118 Not applicable.
31

32 119

33
34 120 **Ethics approval**

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36 121 This study was approved by the UK National Research Ethics Authority (14/LO/1169) and
37 122 conducted in accordance with the World Medical Association's Code of Ethics (Declaration
38 of Helsinki).
39 123

40 124

41
42
43 125 **Consent to participate**

44 126 Written informed consent was given by children's carer(s) at recruitment into the study.
45

46 127

47
48 128 **Consent for publication**

49 129 Not applicable.
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136 **Introduction**

137 Postnatal depression affects approximately 12% of mothers worldwide.¹ In contrast to ‘baby
138 blues’, which is a state of emotional lability that affects between 13.7%-76.0% of women in
139 the first few days after birth and typically resolves spontaneously within two weeks,²
140 postnatal depression is more severe and starts in the first few months post-partum¹. Stressful
141 life events have been linked to a heightened risk of developing postnatal depression;³ for
142 example, mothers of preterm infants have a significantly higher risk of postpartum depression
143 compared to mothers of term infants,⁴ likely due to heightened stress associated with
144 perinatal complications.⁵

145
146 Women with postnatal depression tend to be less responsive to their baby’s needs and to
147 display less affection.⁶ Therefore, in the short-term postpartum depression may affect mother-
148 infant interactions⁷ and in the long-term it may lead to alterations in brain development,⁸
149 emotional difficulties,⁹ less secure attachment, cognitive and behavioural problems in
150 childhood, and a possible increased risk of autism spectrum disorder (ASD).^{10,11} Large cohort
151 studies, such as the Avon Longitudinal Study of Parents and Children (ALSPAC), have
152 shown that these associations are even evident when maternal depression is measured on a
153 continuum of symptoms rather than a dichotomous diagnosis,¹²⁻¹⁴ supporting the notion that
154 elevated sub-diagnostic psychiatric symptoms can also negatively impact on children’s
155 development.¹⁵

156
157 Studies investigating the underlying causes that may link maternal postnatal depression to
158 child outcomes have implicated several biological and environmental variables. For instance,
159 genetic and epigenetic factors have been shown to both mediate and mitigate the
160 intergenerational transmission of psychiatric disorders,¹⁶ while lower quality parenting,
161 interparental conflict, and socioeconomic deprivation have been shown to exacerbate
162 children’s developmental risk of emotional and behavioural problems.¹¹ In addition, being
163 born preterm (i.e. <37 weeks’ gestation, as per the World Health Organization definition¹⁷)
164 has been associated with alterations in early brain development,¹⁸ as well as neurological,
165 behavioural and cognitive problems in childhood and beyond.^{19,20} Therefore, it is complex to
166 disentangle the possible effects of postnatal maternal mental health and those of perinatal
167 clinical factors on specific outcomes in preterm children, as these may involve both maternal
168 psychosocial and biological variables, as well as child preterm-related neurodevelopmental
169 morbidity.

170

171 Furthermore, a question that remains unanswered is whether preterm birth accentuates the
172 association between maternal postnatal depression and child outcome. Two theoretical
173 frameworks exist that hypothesise certain infants may be influenced differently by external
174 stimuli: the diathesis stress model proposes that certain vulnerability factors make affected
175 infants more prone to suboptimal environmental influences with subsequent poorer
176 outcomes,^{21,22} whereas the differential susceptibility model frames such factors as plasticity-
177 mediating, thus leading to poorer outcomes in negative environments, as well as better
178 outcomes in supportive environments.^{22,23} Previous studies investigating differential
179 susceptibility have shown mixed findings studying a range of environmental and clinical
180 exposures,^{24,25} with child outcomes including attachment, internalising and externalising
181 behaviour, and academic competence.²⁵ Both low birthweight in term infants (small for
182 gestational age, SGA)²⁶ and preterm birth (PTB)^{23,24,27} have been explored as distinct
183 potential susceptibility factors. This distinction is based on the different pathophysiological
184 processes underlying the respective conditions of SGA and PTB, both, or a combination, of
185 which can cause low birthweight.²⁸ For example, SGA is a marker of intra-uterine growth
186 restriction related to placental dysfunction,²⁹ whereas PTB can be caused by a multitude of
187 factors, including infection and inflammation.³⁰

188

189 Given that mothers of preterm children experience elevated levels of distress,³¹ are at high
190 risk of developing postnatal depression,³² and that preterm children themselves are vulnerable
191 to psychiatric sequelae,³³ in addition to investigating the association between very early
192 maternal postnatal depressive symptoms and child behavioural and emotional outcomes, we
193 further aimed to investigate the interaction between preterm birth and maternal depressive
194 symptoms on child outcomes. Previous work focusing on the differential susceptibility of
195 preterm born children to various environmental stimuli, as described above, had not yet
196 studied maternal depressive symptoms as a proposed exposure. We specifically aimed to
197 investigate the continuum of maternal depressive symptoms rather than solely focussing on
198 clinically significant maternal depression, so as to provide more nuanced information about
199 the importance of subclinical depressive symptoms on child outcomes. We hypothesised that
200 early postnatal maternal depressive symptoms would be more elevated in mothers of preterm
201 compared to term infants and that these would impact preterm children's behavioural and
202 emotional outcomes to a greater degree than their term counterparts.

203

204 **Methods**

205 **Sample**

206 Participants were enrolled in the Developing Human Connectome Project (DHCP,
207 <http://www.developingconnectome.org/>), a neuroimaging-focused project, with eligibility
208 criteria including pregnant women (aged ≥ 16 years) with a gestational age of 20–42 weeks,
209 and newborn infants aged 24–44 weeks; infants enrolled in the DHCP had magnetic
210 resonance imaging (MRI) at term-equivalent age. Exclusion criteria for the DHCP included:
211 contraindications to MRI, babies being too unwell to tolerate a scan, and language difficulties
212 preventing informed consent.³⁴ Toddlers were invited to the Centre for the Developing Brain,
213 St Thomas' Hospital, London, for neurodevelopmental assessment at 18 months post-
214 expected delivery date; appointments were made according to family availability as close as
215 possible to this time-point. Inclusion criteria for our follow-up study were: mother and baby
216 attendance for MRI at term-equivalent age; completed toddler neurodevelopmental
217 assessment. These inclusion criteria were met by 509 toddlers by the date of closure for this
218 analysis (26/02/2020). Of the 509 toddlers, 51 were one of a twin pregnancy, and three were
219 one of a triplet pregnancy; the sample contained 22 sibling pairs and one set of triplets. This
220 study was approved by the UK National Research Ethics Authority (14/LO/1169) and
221 conducted in accordance with the World Medical Association's Code of Ethics (Declaration
222 of Helsinki). Written informed consent was given by children's carer(s) at recruitment into
223 the study.

225 **Maternal variables**

226 Maternal age, parity, Body Mass Index (BMI), ethnicity and postcode were collected at
227 enrolment into the DHCP study. Our sample was ethnically representative of the surrounding
228 geographical area. Parity was coded as 0, 1, 2, or ≥ 3 previous children. Index of Multiple
229 Deprivation (IMD) rank was computed from the current maternal postcode using the 2019
230 IMD classification; it combines locality-specific information about income, employment,
231 education, health, crime, housing and living environment, thus providing a proxy for family
232 socioeconomic status.³⁵ Lower IMD rank corresponds to greater social deprivation. Our
233 sample was generally less deprived than the surrounding geographical areas, as well as the
234 UK as a whole, reflecting trends observed in other UK longitudinal studies.³⁶

236 *Maternal depressive symptoms* were measured using the Edinburgh Postnatal Depression
237 Scale (EPDS)³⁷ on the day of infant's MRI at term-equivalent age. Mothers of infants born at

1
2
3 238 term were tested in the first few weeks postnatally, whereas mothers of preterm-born infants
4
5 239 were tested once they reached term-corrected age. The EPDS is a 10-item screening
6
7 240 questionnaire completed by mothers, with higher scores reflecting a higher likelihood of
8
9 241 depressive disorders. A score of 13 can be used as a cut-off indicating high-level symptoms,
10
11 242 although a cut-off of 11 maximises the sensitivity and specificity of the screening tool for
12
13 243 depression.³⁸ Mothers completed the EPDS independently in a private room in our Centre,
14
15 244 with no interaction with the researcher. Participants were informed that the results would be
16
17 245 discussed with them, and consented to information being shared with their General
18
19 246 Practitioner in the case of high scores. The EPDS questionnaire was scored by a member of
20
21 247 the DHCP team.³⁴
22
23 248

249 Child variables

24 250 Infant *clinical characteristics* were gathered from clinical notes where available, or from
25
26 251 maternal report, and included: sex, gestational age at birth, birth weight, and pregnancy size
27
28 252 (singleton/twin/triplet).
29
30 253

31 254 *Behavioural outcomes* were assessed using the Child Behaviour Checklist/1^{1/2}-5 (CBCL), a
32
33 255 parent-completed 100-item questionnaire, in which the parent rates the child's behaviour over
34
35 256 the preceding two months using a 3-point Likert scale ("not true", "somewhat or sometimes
36
37 257 true", and "very true or often true"). Responses are categorised into syndrome profiles, and
38
39 258 these are subsequently grouped into internalising (emotional reactivity, anxiety/depression,
40
41 259 somatic complaints, and withdrawal), externalising (attention problems, aggressive
42
43 260 behaviour) and total (internalising, externalising, sleep and other) problem scales. Higher
44
45 261 scores indicate increased emotional and behavioural problems. Total scores are classified into
46
47 262 a normal range (<83rd centile, T <60), borderline range (83rd-90th centile, T 60-63), and
48
49 263 clinical range (>90th centile, T ≥64).³⁹ The CBCL is known to have high reliability, validity
50
51 264 and cross-informant agreement for measuring children's emotional and behavioural
52
53 265 problems.³⁹
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55 266

56 267 We used the Quantitative Checklist for Autism in Toddlers (Q-CHAT) as an additional
57
58 268 behavioural screening tool to broaden the exploration of mental health outcomes in toddlers.
59
60 269 The Q-CHAT is a parent-completed 25-item questionnaire, in which the child's behaviour is
270
271 270 scored on a 5-point (0-4) frequency scale. Higher total scores correspond to a higher
frequency of behaviours also observed in autism spectrum conditions. The Q-CHAT shows

272 good test-retest reliability, face validity and specificity, yet poor positive predictive value for
273 autism,^{40,41} highlighting that higher Q-CHAT scores may reflect developmental immaturity
274 rather than autism.⁴¹

275
276 *Cognitive assessment* was performed using the Bayley Scales of Infant and Toddler
277 Development – Third Edition (Bayley-III). The Bayley-III provides scores for a child's
278 overall cognitive, language and motor development. The cognitive standardised composite
279 score was used in this study; scores between 70-84 indicate mild cognitive impairment,
280 scores between 55-69 indicate moderate impairment, and scores lower than 55 indicate severe
281 impairment⁴². Reliability and validity of the Bayley-III have been shown to be robust,⁴³
282 although some studies report its underestimation of developmental problems.⁴⁴

284 Assessments were carried out by staff experienced in the neurocognitive assessments of
285 toddlers.

287 Analysis

288 Descriptive statistics and one-way ANOVA tests were performed in IBM SPSS Statistics for
289 Windows v.25. All other analyses were carried out in Stata v.16.

291 Multiple imputation (MI) was carried out to account for missing data in CBCL (11/509,
292 2.24%), Q-CHAT (9/509, 1.8%), maternal EPDS (73/509, 14.3%), maternal BMI (27/509,
293 5.3%) and IMD rank (3/509, 0.6%). Variables were imputed simultaneously using the 'mi
294 impute chained' procedure that performs imputation by chained equations. The imputation
295 models had the same structural form as the analysis models, and included all variables that
296 appear in the corresponding analysis models (maternal EPDS, maternal BMI, multiple
297 pregnancy, parity, IMD rank, gestational age at birth, birthweight, sex, corrected age at
298 assessment, and Bayley III Cognitive Composite score); in addition, maternal age was also
299 included in the imputation model because it was found to be a significant predictor of both
300 the total CBCL raw score and the Q-CHAT score when it was included as the sole
301 independent variable in linear regression models.

303 Maternal EPDS and CBCL were imputed using Poisson regression; Q-CHAT, maternal BMI,
304 and the IMD rank were imputed using linear regression. 40 MI datasets were created. To
305 assess the stability of our MI parameters, we extracted the Monte Carlo error of each

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3 306 parameter estimate and examined whether the error for the coefficient was less than 10% of
4
5 307 the parameter's standard error estimate. MI estimates were used for the primary analyses and
6
7 308 compared to the estimates from complete-case (CC, individuals who had no missing data pre-
8
9 309 imputation) analyses. Normal probability plots of residuals from the CC analyses were
10
11 310 examined.

12 311
13 312 The analysis models were multiple linear regressions fitted using the 'mi estimate' procedure,
14
15 313 which estimates effects after application of Rubin's rules.⁴⁵ To account for the small amount
16
17 314 of clustering in our data (twin/triplet siblings), the models' standard errors were obtained
18
19 315 using Stata's robust cluster estimator 'vce(cluster *idvar*)'. For continuous variables, Cohen's
20
21 316 f-squared effect sizes were calculated using $f^2 = (R_{AB}^2 - R_A^2)/(1 - R_{AB}^2)$, where R_{AB}^2 is the R-
22
23 317 squared value from a regression model that includes the variable of interest as well as all the
24
25 318 covariates used in the model, and R_A^2 is the R-squared value from the regression model that
26
27 319 includes only the covariates.^{46,47} For binary variables, Cohen's f-squared effect sizes were
28
29 320 produced after estimating first the Cohen's d using the formula: $f^2 = \frac{d}{2k}$, where k is the
30
31 321 number of groups. As a measure of dispersion, Cohen's d used the average root mean-square
32
33 322 error over the MI datasets. Adjusted R-squared values after MI were extracted after
34
35 323 estimating the model with the user-written 'mibeta' command with the 'fisherz' option,⁴⁸
36
37 324 which calculates R-squared measures for linear regression with MI data. The significance of
38
39 325 the joint effect of the categorical variable parity was assessed using 'mi test' which performs
40
41 326 Wald tests of composite linear hypotheses.

42 327
43 328 *Primary outcome measures* were children's total CBCL raw score and Q-CHAT score.
44
45 329 *Secondary outcome measures* were CBCL internalising and externalising scores. The effect
46
47 330 of maternal EPDS score was adjusted for IMD rank, maternal age, maternal BMI, maternal
48
49 331 parity, pregnancy size, and the following child's variables: continuous gestational age, birth
50
51 332 weight, Bayley-III cognitive composite score, and corrected age at assessment. The
52
53 333 interaction between preterm birth and maternal depressive symptoms was explored using a
54
55 334 complete case analysis in both CBCL and Q-CHAT models, using a dichotomised measure of
56
57 335 gestational age. EPDS, CBCL and Q-CHAT scores were compared between term (≥ 37 weeks
58
59 336 gestation) and preterm infants (< 37 weeks gestation) using the complete case dataset. Our
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337 regressions were thus run twice: with and without the interaction term.
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5 340 As all mothers had their EPDS score measured near term (or term-corrected in the case of
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7 341 mothers of preterm infants), we further investigated the association between time elapsing
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9 342 between baby's birth and mother's EPDS assessment and EPDS score, in order to avoid
10
11 343 erroneously identifying 'baby blues' in mothers of term-born infants versus postnatal
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13 344 depression in mothers of preterm infants. This post-hoc analysis was performed using
14
15 345 Poisson regression.

16 346

17 347 Patient and Public Involvement

18
19 348 The current study was developed in consultation with the Weston Programme for Family
20
21 349 Centered Research, which involves parents to define what research is valuable to them, and to
22
23 350 allow them to lead it with support from the scientists in the Centre for the Developing Brain.

24 351

25 352 Results

26 353 Descriptive statistics

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29 354 Our sample of 509 toddlers were followed up at a median corrected age of 18.4 months
30
31 355 (range 17.3 – 24.3 months). 51 (10.0%) of these were twins, and 3 (0.59%) were triplets. Of
32
33 356 the 509, 21 (4.13%) mothers scored above a clinical cut-off (≥ 13) on the EPDS;(26) the
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35 357 distribution of maternal EPDS scores is shown graphically in Supplementary Figure 1.
36
37 358 Demographic data are shown in Table 1. Complete data were available for 400 (78.6%)
38
39 359 participants. Missing data were imputed and thus all 509 subjects were included in the
40
41 360 primary and secondary analyses. One participant was excluded from the cognition analysis
42
43 361 after examining the quintiles of the residuals against the theoretical quintiles of a normal
44
45 362 distribution. The mean CBCL T score was 46.9 (SD 9.5) (Table 1); using CBCL-specified
46
47 363 cut-offs,³⁹ 449 (90.2%) of participants had a CBCL score in the normal range, 30 (6.0%)
48
49 364 were borderline, and 19 (3.8%) scored in the clinical range. The mean Q-CHAT score was
50
51 365 30.5 (SD 9.3) (Table 1). The mean Bayley III Cognitive Composite score in our sample was
52
53 366 100 (SD 11.4) (Table 1), which corresponds to the standardised test mean;⁴² 480 (94.3%) of
54
55 367 participants had a normal cognitive score, 24 (4.7%) had mild impairment, 5 (1%) had
56
57 368 moderate impairment, and nil had severe impairment. This distribution is not dissimilar from
58
59 369 that of the normative sample.⁴²

60 370

61 371 Association between maternal EPDS score and toddler CBCL and Q-CHAT scores

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2
3 372 Predictors of children's CBCL and Q-CHAT scores after multiple imputation are shown in
4 373 Table 2. Higher maternal EPDS score was associated with children's higher CBCL Total
5 374 score (B=0.93, 95% CI 0.43-1.44, $p<0.001$, $f^2=0.05$) and Q-CHAT score (B=0.27, 95% CI
6 375 0.03-0.52, $p=.031$, $f^2=0.01$) (Table 2). These associations are presented graphically in Figure
7 376 1 and Figure 2, respectively. Boys had higher CBCL and Q-CHAT scores than girls. Higher
8 377 Q-CHAT scores were associated with lower IMD rank (i.e., greater socio-economic
9 378 deprivation) and lower Bayley-III cognitive composite scores. Parity was not a significant
10 379 predictor of outcome in any of the models (Table 2).

380

11 381 Maternal EPDS score did not disproportionately affect preterm children with respect to
12 382 CBCL or Q-CHAT scores (Table 3).

383

13 384 Association between maternal EPDS score and toddler CBCL internalising and externalising
14 385 scores

15 386 Higher maternal EPDS score was associated with both internalising (B=0.22, 95% CI 0.08-
16 387 0.36, $p<0.01$, $f^2=0.03$) and externalising (B=0.40, 95% CI 0.20-0.61, $p<0.001$, $f^2=0.05$)
17 388 symptoms in children (Supplementary Table 1 and 2, respectively). Comparison of the
18 389 imputed model analyses to the complete-case analyses showed that results were consistent for
19 390 the CBCL model (Supplementary Table 3). Comparison for the Q-CHAT model showed that
20 391 maternal EPDS was a significant predictor in the imputed model, but not in the complete-case
21 392 analysis (Supplementary Table 3).

393

22 394 Effect of time-lag between baby's birth and mother's EPDS assessment and EPDS score

23 395 Mothers who gave birth prematurely (<37 weeks gestation) had their EPDS score assessed on
24 396 average 7.7 weeks later post-delivery than mothers who gave birth at term (preterm
25 397 participants M=8.9 (SD 4.8), term participants M=1.2 (SD 1.3); $t(99.4)=15.5$, $p<.001$). The
26 398 time-lag between birth and EPDS assessment did not predict maternal EPDS score, and there
27 399 was no evidence of a significant interaction between gestation and birth-to-assessment time-
28 400 lag (Supplementary Table 4 and 5, respectively).

401

29 402 **Discussion**

30 403 **Principal findings**

31 404 Our results showed that more maternal self-reported depressive symptoms shortly after birth
32 405 were associated with greater parent-reported toddlers' behavioural problems. Given that

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2
3 406 fewer than 5% of the mothers in our cohort had EPDS scores above a clinical threshold,³⁷ our
4 407 findings indicate that even subclinical depressive symptoms – i.e. not only diagnostic
5 408 postnatal depression – adversely impact children’s behavioural outcomes. In addition, our
6 409 cohort was typically developing with few CBCL scores reaching a concerning threshold; our
7 410 results could be interpreted within the conceptual framework of mental illness lying on a
8 411 continuum with typical behavioural traits.⁴⁹ Our findings further showed that preterm birth
9 412 did not influence the association between self-reported maternal depressive symptoms and
10 413 parent-reported infants’ behavioural outcomes in toddlerhood. This indicates that in this
11 414 context preterm birth may not be regarded as a vulnerability or plasticity factor. Interestingly,
12 415 mothers of preterm infants did not report more depressive symptoms compared to mothers of
13 416 term infants in this study.
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417

418 **Comparison to prior literature**

419 Our results with respect to internalising and externalising symptoms are in line with previous
420 studies, including large population cohort studies, that showed an association between
421 postnatal maternal depression and young children’s emotional and behavioural problems.¹¹
422 Another previous study in 18-month old toddlers found that maternal depression was
423 associated with internalising and dysregulated behaviour, but not externalising symptoms.⁵⁰
424 This difference between our and Conroy et al.’s findings may have arisen from their
425 exclusion of infants born <36 weeks and their use of a clinical diagnosis of depression for
426 mothers, rather than the continuous self-reported approach we employed. Interestingly, our
427 finding that even subclinical depressive symptoms may adversely impact parent-reported
428 child behavioural outcomes is in line with recent data showing that low- as well as high-level
429 depressive symptoms are associated with internalising and externalising symptoms in
430 children aged 3 years.⁵¹
431

432

433 The results showing an association between maternal postnatal depressive symptoms and the
434 Q-CHAT are less robust and need to be interpreted with caution. Firstly, these results must be
435 viewed in the context of the Q-CHAT having a low positive predictive value for autism, with
436 the measure perhaps being more reflective of developmental immaturity.⁴¹ Although some
437 prior studies have shown an association between antenatal maternal depression and
438 offspring’s ASD,^{10,52} and postnatal depression has been suggested as a potential focus of
439 cross-domain studies of ASD,⁵³ there is no clear aetiological role of maternal postnatal
depression in the development of ASD *per se*. Also, given that mothers with ASD are more

1
2
3 440 likely to suffer from perinatal depression than mothers without ASD,⁵⁴ and ASD is highly
4
5 441 heritable,⁵⁵ maternal depression may actually be a confounding rather than causative factor in
6
7 442 our observed results. Overall, therefore, our findings with respect to the Q-CHAT do not
8
9 443 provide support for a role of maternal depression in the aetiology of autism traits, but rather
10
11 444 suggest that maternal depression can influence toddler behaviour.
12

13
14 446 The finding that preterm infants were not disproportionately affected by maternal depressive
15
16 447 symptoms supports Hadfield et al.'s findings that maternal distress at 9 months did not
17
18 448 differentially impact very preterm (<34 weeks) or late preterm (34-36⁺⁶ weeks) infants with
19
20 449 respect to socioemotional outcomes, although paternal distress did have an impact on very
21
22 450 preterm infants' outcomes.²⁴ However, our results differ from Gueron-Sela et al.'s finding
23
24 451 that very preterm (28-33 weeks) 12 month old infants' social outcomes were more influenced
25
26 452 by maternal emotional distress at 6 months than term infants' outcomes.²³ The inconsistent
27
28 453 findings may be due to methodological differences: for instance, our infant assessment being
29
30 454 conducted at 18 months corrected age when social competency is more developed, our
31
32 455 assessment of maternal depressive symptoms being in the very early postnatal period, or our
33
34 456 use of the CBCL and Q-CHAT tools as markers of toddler behaviour. Importantly, the lack of
35
36 457 support for a diathesis-stress or differential susceptibility model of maternal mental state on
37
38 458 preterm infants in our study must be viewed in the context of our results also showing no
39
40 459 difference in CBCL and Q-CHAT scores between term and preterm infants. This is in
41
42 460 contrast to the existing literature that preterm infants are more likely than term infants to
43
44 461 develop behavioural problems, such as ADHD, in childhood and adolescence.^{20,33} It is
45
46 462 possible that the phenotypes of neurodevelopmental and neuropsychiatric disorders assessed
47
48 463 with the chosen behavioural measures may not be sufficiently expressed at 18 months
49
50 464 corrected age.⁵⁶ In addition, as briefly discussed above, much of the existing literature
51
52 465 emphasises the risk of extreme (<28 weeks) or very preterm (28-33 weeks) birth on later
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54 466 behavioural outcomes,^{20,33} whereas only 3.5% and 5.5% of our participants fell within the
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56 467 extreme and very preterm group, respectively, and we thus may not have the power to show
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58 468 any subtle effects.
59

59 469 60 **Strengths & limitations of the study**

61 470 The strengths of this study lie primarily in its large sample and prospective data collection.
62
63 471 Moreover, the use of multiple imputation methodology has facilitated retention of a complete
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65 472

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2
3 473 dataset, thus minimising non-response bias and increasing parameter precision. A strength in
4
5 474 comparison to prior population cohort studies is that we assessed very early maternal
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7 475 depressive symptoms, and our sample is perhaps more representative of today's society –
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9 476 with increasing maternal age – than large cohort studies conducted in the 1990s-2000s. Given
10
11 477 the complex interplay of biological and environmental factors in the aetiology of behavioural
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13 478 disorders, the inclusion of a substantive proportion of preterm infants in our cohort also offers
14
15 479 an important insight into the role of preterm birth in behavioural outcomes; moreover, our
16
17 480 results represent the full gestational spectrum, rather than discrete gestational categories. In
18
19 481 addition, using maternal depressive symptoms as a continuous, rather than dichotomous,
20
21 482 variable allows a more nuanced understanding of the role maternal postnatal depressive
22
23 483 symptoms may play in influencing children's outcomes.

484

24 485 There are several limitations to this study that necessitate our findings to be considered with
25
26 486 caution. Firstly, differences in birth-to-EPDS-assessment time-lags are a potential
27
28 487 confounder, given the time-sensitive nature of early-onset temporary baby blues and later-
29
30 488 onset pathological postnatal depression. Mothers of infants born at term were assessed early
31
32 489 post-delivery, within the period one would anticipate baby blues to present, whereas mothers
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34 490 of preterm participants were on average assessed later, when postnatal depression
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36 491 predominates.^{1,57} Although our post-hoc analyses showed that the time elapsed from birth to
37
38 492 EPDS assessment was not associated with maternal EPDS score, providing reassurance that
39
40 493 our assessments of mothers of term-born infants were not inflated by the common temporary
41
42 494 symptoms of baby blues, it is possible that we did not capture the full extent of later-onset
43
44 495 depressive symptoms in mothers of term-born infants. This may explain why maternal EPDS
45
46 496 scores did not differ between preterm and term groups in our complete dataset analysis,
47
48 497 contrary to the current literature,³¹ as well as why our rate of postpartum depression, using an
49
50 498 EPDS cut-off of 13, was low (4.1%) compared to the previously documented UK community
51
52 499 prevalence rate of 8.9% at eight weeks postpartum.⁵⁸ Our results must therefore be
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54 500 interpreted with some caution.

501

53 502 Secondly, although statistical techniques were used to impute missing data and mitigate this
54
55 503 problem, 14.3% of maternal EPDS scores were missing. This rate of missingness may relate
56
57 504 to some mothers being reluctant to complete a questionnaire at the time their child is having
58
59 505 an MRI, or due to simultaneous childcare duties. Thirdly, a number of important confounders
60
506 that are likely to affect children's behavioural outcomes were not assessed in this study,

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3 507 including genetic risk for psychiatric disorders,⁵⁹ parental psychiatric co-morbidities,⁵⁰
4 508 chronicity of postnatal depressive symptoms,⁵¹ antenatal maternal depression, paternal
5 509 depression and subsequent parent-infant attachment, and inter-parental conflict.¹¹ Thus, we
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7
8 510 are unable to conclude whether our observed associations between early postnatal maternal
9
10 511 depressive symptoms and children's behavioural outcomes are moderated or mediated by
11
12 512 other parental and/or psychiatric factors.

13
14 513

15 514 Fourthly, whilst our study included a reasonable proportion of preterm infants (97/509, 19%),
16
17 515 our sample was not random, as preterm children were selectively recruited for the DHCP;
18
19 516 indeed, preterm infants are over-represented in our sample when compared to the UK
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21 517 population incidence (7.3%),⁶⁰ which may limit the study's generalisability to the general
22
23 518 population. This over-representation of preterm infants may explain why our mean maternal
24
25 519 age is higher than the national mean age of 30.7,⁶¹ given that increasing maternal age is
26
27 520 associated with increased risk of adverse pregnancy outcomes.⁶² Our observed large maternal
28
29 521 age range in itself also poses a limitation on the generalisability of our findings to the general
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31 522 population, and further research would be necessary to identify a possible moderation effect
32
33 523 of high maternal age on both EPDS scores and child behavioural outcomes. Furthermore,
34
35 524 although a 19% prevalence of preterm birth is high for a community sample, the proportion
36
37 525 of very and extreme preterm infants in our sample is small, and this may not have provided
38
39 526 sufficient power to detect any differential susceptibility effect of preterm birth on outcomes.

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42 528 Sixthly, the effect sizes of the association between maternal EPDS score and behavioural
43
44 529 problems were small; this raises questions regarding the clinical significance of our findings
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46 530 and potentially explains some of the inconsistency between this and previous studies. Even
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48 531 within our analyses, the association between maternal depressive symptoms and Q-CHAT
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50 532 scores was not observed in our complete case analysis, thus calling into question the validity
51
52 533 of this result. It is also important to highlight again the poor positive predictive value of the
53
54 534 Q-CHAT for autism;⁴¹ higher Q-CHAT scores do not imply a diagnosis of ASD, and this
55
56 535 distinction may also explain the contrast to previous studies.

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58 536

59 537 Finally, it is well documented that maternal depression influences reporting of Q-CHAT ⁶³
60
538 and CBCL scores.⁶⁴ Our study used maternal report of maternal depressive symptoms, and
539
540 539 our outcome measures were parent-completed questionnaires; despite the CBCL showing

540 good cross-informant agreement,³⁹ it is thus possible that reporting bias with common
541 method variance could have skewed our results.

542

543 **Implications of our findings**

544 Of greatest importance to clinicians and policymakers is our finding that even *subclinical*
545 self-reported maternal depressive symptoms are associated with parent-reported behavioural
546 outcomes of offspring. This has significant implications for the risk-stratification of women
547 and their babies in the postnatal period, during which contact with medical professionals is
548 already established. Identifying high risk families and providing appropriate supportive
549 measures at the early postnatal stage may help to prevent future psychiatric morbidity.

550

551 **Future research**

552 Further follow-up of large cohorts of preterm and term infants, to an age when behavioural
553 phenotypes may become more pronounced, is needed to investigate whether the long-term
554 developmental trajectories of term and ex-preterm infants are differentially susceptible to
555 changes of postnatal maternal mental health. Future research should consider both maternal
556 and paternal mental health, as well as socioeconomic and environmental factors on child
557 outcomes. Such follow-up should use independent, objective assessments of child
558 behavioural outcomes in order to avoid the common method variance inherent to parent-
559 reported measures. Finally, it is crucial for future research to elucidate the interplay of
560 biochemical and neurodevelopmental changes that may mediate and confound the translation
561 of environmental exposures into distal behavioural phenotypes.

562

563 **Conclusion**

564 This prospective longitudinal cohort study found no evidence to support the concept of
565 preterm birth as a vulnerability or plasticity factor with respect to the effect of maternal
566 depressive symptoms on behavioural development. However, we showed that early
567 subclinical maternal postnatal depressive symptoms were associated with behavioural
568 problems in children on parent-reported measures. This adds to the increasing body of
569 literature indicating the role of subclinical and early postnatal depressive symptoms in the
570 aetiology of childhood behavioural disorders. These findings are of great relevance to child
571 and public health, and further research may strengthen its implications for developing
572 strategies to facilitate effective screening and support for women and children, enabling all to
573 reach their full potential.

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5 575

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15 581

17 582 **Conceptualization:** SC, ADE, CN; **Methodology:** IK, GV, SC, AP, ADE, CN;

18
19 583 **Investigation:** SF, AC; **Data curation:** IK, AL; **Formal analysis:** IK, GV, AP, CN;

20 584 **Writing – original draft preparation:** IK; **Writing – Review & Editing:** GV, AL, SF, AC,

22 585 SC, AP, ADE, CN; **Visualisation:** IK, GV; **Funding acquisition:** SC, ADE; **Supervision:**

24 586 AP, ADE, CN.

25 587

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768 **Table 1: Socio-demographic, maternal and clinical characteristics (n=509)**

Variable	Number (%)*
Sex: Male	274 (53.8)
Index of Multiple Deprivation (IMD) quintiles	
1 (least deprived) ^a	65 (12.8)
2	87 (17.2)
3	108 (21.3)
4	173 (34.2)
5 (most deprived)	73 (14.4)
Gestational age at birth (weeks), median [range]	39.7 [20 – 43]
Gestational category	
Extremely preterm (<28 weeks)	18 (3.5)
Very preterm (28-32 weeks)	28 (5.5)
Late preterm (32-37 weeks)	51 (10.0)
Term (≥37 weeks)	412 (80.9)
Birthweight (g), median [range]	3290 [450 – 4750]
Multiple pregnancy	54 (10.6)
Maternal parity	
0	332 (65.2)
1	124 (24.4)
2	32 (6.3)
3+	21 (4.2)
Maternal BMI (kg/m ²), median [range]	23.2 [15.3 – 43.6]
Maternal age at infant's birth (years), mean (SD) [range]	34.2 (4.8) [17 – 52]
Maternal ethnicity	
White	272 (53.4)
Black/Black British	56 (11.0)
Asian/Asian British	28 (5.5)
Chinese	18 (3.5)
Mixed – White & Asian	4 (0.8)
Mixed – White & Black	4 (0.8)
Any other	30 (5.9)
Do not wish to answer	9 (1.8)
No data	88 (17.3)
Bayley III cognitive composite score, mean (SD) [range]	100 (11.4) [55 – 125]
CBCL total T score, mean (SD) [range]	46.9 (9.5) [28 – 69]
Q-CHAT total score, mean (SD) [range]	30.5 (9.3) [8 – 70]
EPDS score, median [range]	4 [0 – 28]
EPDS score, n (%)	
<13	415 (8.2)
≥13	21 (4.1)
No data	73 (14.3)

769 ^a Quintile 1 corresponds to the highest, least deprived, IMD rankings.

770 * unless otherwise specified

Table 2: CBCL and Q-CHAT model predictors using multiple imputation without interaction. (Cf. Supplementary Table 3 for complete case analysis)

	CBCL			Q-CHAT		
	B [95%CI]	p	f ²	B [95%CI]	p	f ²
Maternal EPDS	0.93 [0.43, 1.44]	<.001 ***	0.05	0.27 [0.03, 0.52]	.031 *	0.01
Maternal BMI	-0.09 [-0.44, 0.26]	.621	-	0.06 [-0.13, 0.24]	.538	-
Multiple pregnancy	3.15 [-3.07, 9.37]	.320	-	1.33 [-2.62, 5.28]	.509	-
Parity						
1	-2.52 [-5.96, 0.93]	.151	-	-2.14 [-4.02, -0.27]	.025 ^a	-
2	-3.23 [-9.16, 2.70]	.285	-	0.88 [-1.99, 3.75]	.548	-
3+	-1.37 [-8.36, 5.61]	.699	-	-0.49 [-4.57, 3.60]	.815	-
IMD rank	-1.48 [-3.33, 0.37]	.117	-	-1.50 [-2.60, -0.40]	.008 **	0.02
Gestational age at birth (weeks)	0.10 [-0.65, 0.85]	.786	-	0.26 [-0.17, 0.70]	.233	-
Birthweight (kg)	0.56 [-2.65, 3.78]	.731	-	-1.24 [-2.93, 0.46]	.151	-
Sex:female	-4.14 [-6.96, -1.31]	.004 **	0.06	-1.95 [-3.42, -0.48]	.009 **	0.05
Corrected age at assessment (months)	-0.90 [-2.17, 0.37]	.166	-	-0.16 [-0.91, 0.59]	.677	-
Cognition	-0.05 [-0.20, 0.09]	.467	-	-0.27 [-0.35, -0.20]	<.001 ***	0.12

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL model adjusted R² = 0.0676. Q-CHAT model adjusted R² = 0.193.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

^a Wald test of whole parity variable in Q-CHAT model: F(3, 476.9) = 1.88, p = .133

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.⁴⁶

- indicates data not given, as predictor not significant to 0.05.

Table 3: CBCL and Q-CHAT model predictors using complete case analysis with interaction of ‘EPDS x term’.

	CBCL		Q-CHAT	
	B [95%CI]	p	B [95%CI]	p
Maternal EPDS	0.89 [-0.24, 2.02]	.121	0.24 [-0.28, 0.75]	.365
Maternal BMI	-0.01 [-0.39, 0.37]	.955	0.00 [-0.16, 0.17]	.982
Multiple pregnancy	1.76 [-6.65, 10.17]	.681	0.97 [-2.07, 4.01]	.532
Parity				
1	-2.75 [-6.49, 0.99]	.149	-1.42 [-3.30, 0.46]	.139
2	-3.49 [-10.36, 3.37]	.317	0.16 [-2.84, 3.16]	.917
3+	-1.17 [-9.69, 7.35]	.788	-1.13 [-4.24, 1.98]	.476
IMD rank	-1.41 [-3.54, 0.73]	.195	-1.68 [-2.64, -0.72]	.001 **
Gestation: term	1.25 [-8.34, 10.85]	.797	2.64 [-1.74, 7.02]	.236
Birthweight (kg)	-1.01 [-4.08, 2.05]	.516	-2.25 [-3.73, -0.78]	.003 **
Sex: female	-4.64 [-7.83, -1.44]	.005 **	-2.22 [-3.72, -0.71]	.004 **
Corrected age at assessment (months)	-0.83 [-2.27, 0.62]	.261	-0.39 [-1.18, 0.04]	.335
Cognition	-0.03 [-0.20, 0.14]	.720	-0.22 [-0.29, -0.15]	<.001 ***
EPDS x gestation:term	-0.01 [-1.30, 1.28]	.991	-0.02 [-0.60, 0.56]	.950

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL model adjusted R² = 0.0865. Q-CHAT model adjusted R² = 0.215.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Gestation: term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth.

Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months. EPDS x gestation:term = interaction term between maternal EPDS score and term gestation at birth.

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14 **Fig.1** Children's predicted CBCL scores at 18 months are positively correlated to the
15 maternal EPDS score at term-equivalent age.
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21 **Fig.2** Children's predicted Q-CHAT scores at 18 months are positively correlated to the
22 maternal EPDS score at term-equivalent age.
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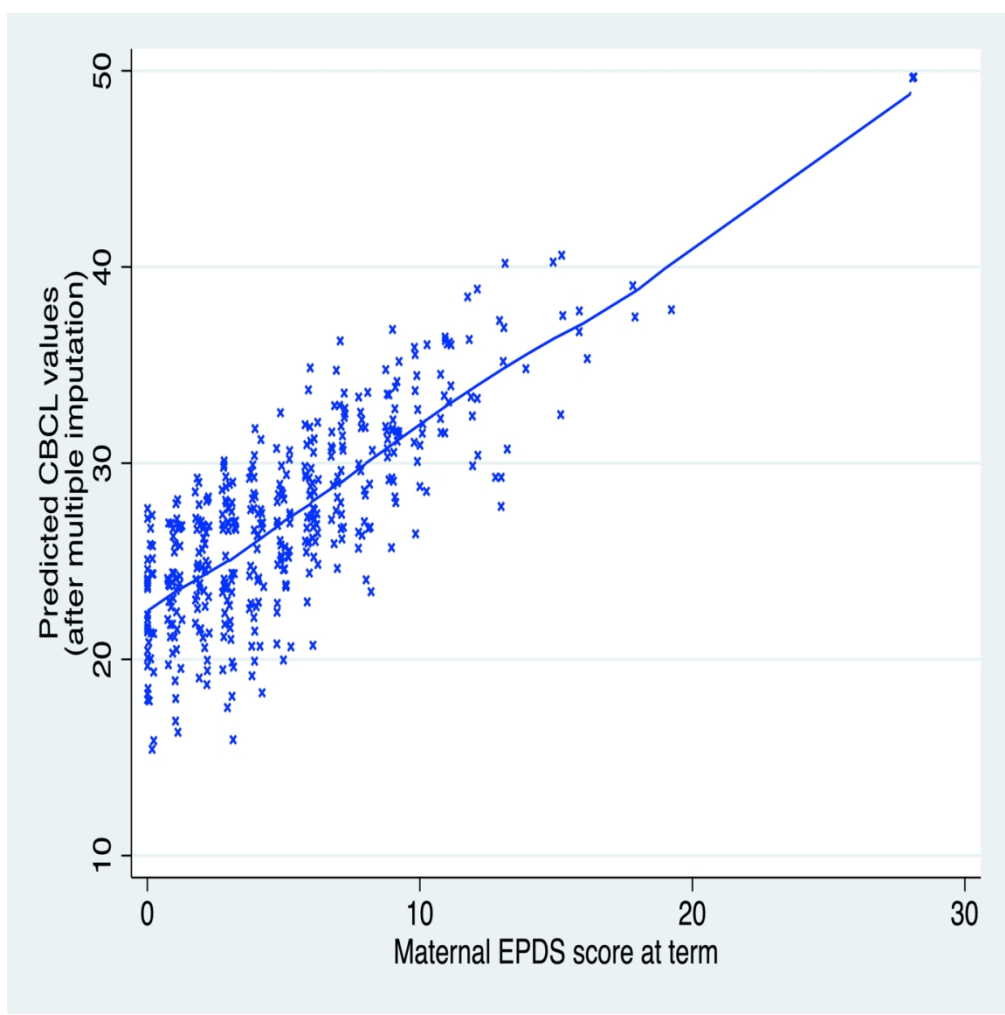


Fig.1 Children’s predicted CBCL scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age

158x158mm (220 x 220 DPI)

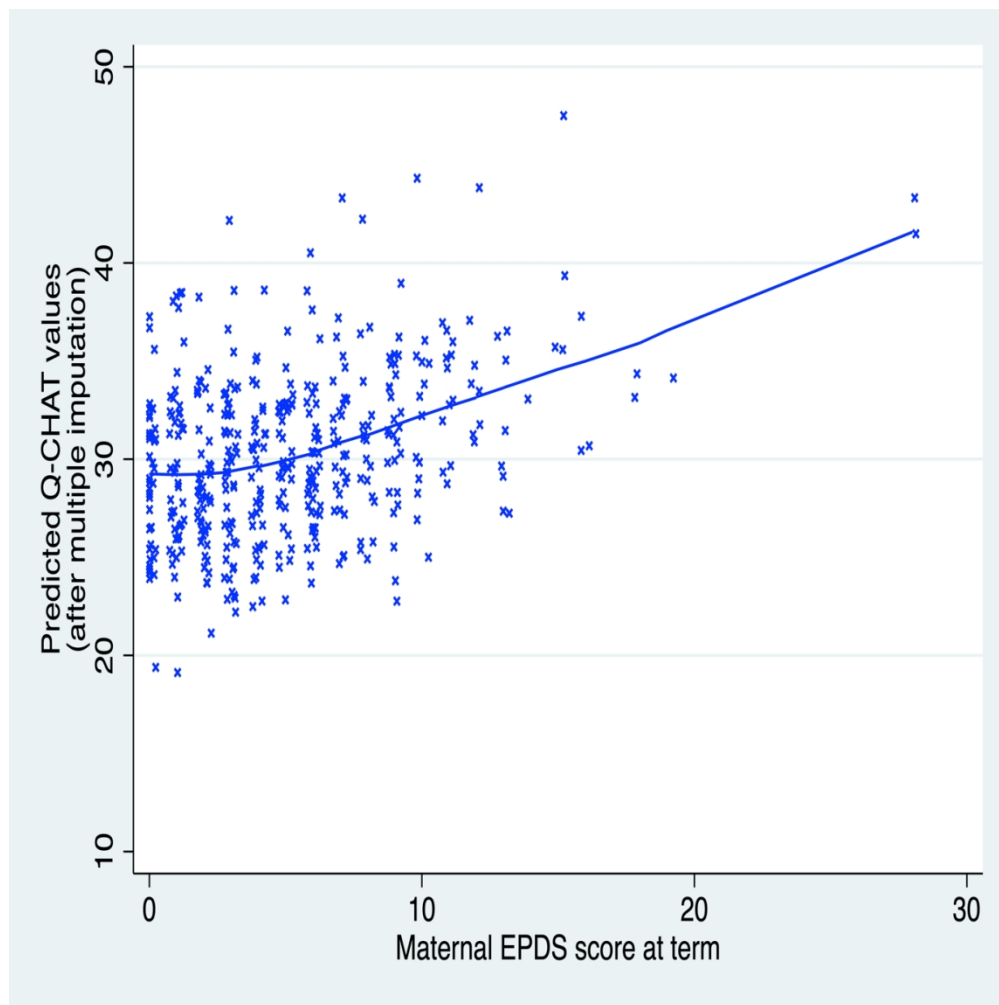


Fig.2 Children’s predicted Q-CHAT scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age.

158x158mm (220 x 220 DPI)

Supplemental material

Supplementary Table 1: CBCL internalising symptom model predictors using multiple imputation.

Supplementary Table 2: CBCL externalising symptom model predictors using multiple imputation.

Supplementary Table 3: CBCL and Q-CHAT model predictors using complete case analysis without interaction.

Supplementary Table 4: EPDS score predictors.

Supplementary Table 5: EPDS score predictors including interaction 'term x time-lag'.

Supplementary Figure 1: Histogram showing the distribution of maternal EPDS scores at term-equivalent age.

Supplementary Table 1: CBCL internalising symptom model predictors using multiple imputation.

	B [95%CI]	p	f²
Maternal EPDS	0.22 [0.08, 0.36]	.003 **	0.03
Maternal BMI	-0.04 [-0.13, 0.06]	.436	-
Multiple pregnancy	0.58 [-1.10, 2.27]	.497	-
Parity			
1	-0.37 [-1.41, 0.67]	.487	-
2	-1.33 [-3.09, 0.42]	.136	-
3+	0.64 [-1.34, 2.62]	.524	-
IMD rank	-0.41 [-0.91, 0.10]	.115	-
Gestational age at birth (weeks)	0.22 [-0.00, 0.44]	.053	-
Birthweight (kg)	-0.97 [-1.90, -0.05]	.038 *	0.005
Sex: female	-0.51 [-1.35, 0.33]	.232	-
Corrected age at assessment (months)	0.02 [-0.41, 0.45]	.923	-
Cognition	-0.05 [-0.10, -0.01]	.016 *	0.01

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.0566.

B = unstandardised coefficient.

Outcome variable = Child Behaviour Checklist internalising sub-score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.¹

- indicates data not given, as predictor not significant to 0.05.

Supplementary Table 2: CBCL externalising symptom model predictors using multiple imputation.

	B [95%CI]	p	f²
Maternal EPDS	0.40 [0.20, 0.61]	<.001 ***	0.05
Maternal BMI	0.01 [-0.17, 0.15]	.933	-
Multiple pregnancy	2.51 [-0.29, 5.31]	.079	-
Parity			
1	-1.06 [-2.53, 0.42]	.160	-
2	-0.61 [-3.55, 2.33]	.682	-
3+	-0.96 [-4.47, 2.56]	.593	-
IMD rank	-0.24 [-1.11, 0.63]	.585	-
Gestational age at birth (weeks)	-0.07 [-0.40, 0.27]	.701	-
Birthweight (kg)	1.03 [-0.38, 2.44]	.153	-
Sex: female	-1.80 [-3.07, -0.53]	.006 **	0.06
Corrected age at assessment (months)	-0.40 [-0.95, 0.16]	.161	-
Cognition	0.03 [-0.03, 0.10]	.322	-

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.0612.

B = unstandardised coefficient.

Outcome variable = Child Behaviour Checklist externalising sub-score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age.

Cognition = infant Bayley III score at 18 months.

Effect size (Cohen’s f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.¹

- indicates data not given, as predictor not significant to 0.05.

Supplementary Table 3: CBCL and Q-CHAT model predictors using complete case analysis without interaction.

	CBCL		Q-CHAT	
	B [95%CI]	p	B [95%CI]	p
Maternal EPDS	0.88 [0.35, 1.41]	.001 **	0.21 [-0.02, 0.44]	.069
Maternal BMI	-0.01 [-0.38, 0.37]	.963	0.01 [-0.16, 0.17]	.930
Multiple pregnancy	1.50 [-6.87, 9.87]	.724	0.43 [-2.50, 3.37]	.772
Parity				
1	-2.83 [-6.60, 0.94]	.141	-1.54 [-3.41, 0.34]	.108
2	-3.49 [-10.3, 3.35]	.316	0.13 [-2.85, 3.10]	.933
3+	-1.38 [-10.0, 7.30]	.755	-1.43 [-4.50, 1.64]	.360
IMD rank	-1.44 [-3.56, 0.67]	.181	-1.75 [-2.70, -0.79]	<.001 ***
Gestational age at birth (weeks)	0.01 [-0.90, 0.91]	.987	0.10 [-0.33, 0.54]	.639
Birthweight (kg)	-0.65 [-4.38, 3.08]	.733	-1.81 [-3.63, 0.00]	.050
Sex: female	-4.57 [-7.82, -1.31]	.006 **	-2.12 [-3.60, -0.64]	.005 **
Corrected age at assessment (months)	-0.84 [-2.26, 0.59]	.247	-0.41 [-1.18, 0.35]	.290
Cognition	-0.03 [-0.20, 0.13]	.689	-0.23 [-0.30, -0.15]	<.001 ***

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL adjusted R² = 0.0862. Q-CHAT adjusted R² = 0.2103.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist externalising sub-score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Gestation (weeks) = dummy variable: 34-36+6 weeks and ≥37 weeks gestation at birth. Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Supplementary Table 4: EPDS score predictors.

	IRR [95%CI]	p
Time-lag (weeks)	1.01 [0.97, 1.05]	.647
Gestation:term	0.91 [0.64, 1.31]	.627
IMD rank	1.00 [1.00, 1.00]	.103
Multiple pregnancy	0.66 [0.46, 0.96]	.031 *
Parity		
1	0.79 [0.66, 0.95]	.011 *
2	0.87 [0.60, 1.28]	.491
3+	0.84 [0.54, 1.31]	.445
Birthweight (kg)	0.98 [0.83, 1.17]	.847
Sex:female	1.13 [0.98, 1.31]	.098

p<0.05 *; p<0.01 **; p<0.001 ***

Pseudo R² = 0.0228

IRR = incidence rate ratio

Outcome variable = maternal Edinburgh Postnatal Depression Scale (EPDS) score at term-equivalent age. Time-lag (weeks) = time in weeks between birth and EPDS assessment. Gestation:term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren).

Supplementary Table 5: EPDS score predictors including interaction 'term x time-lag'.

	IRR [95%CI]	p
Time-lag (weeks)	1.00 [0.97, 1.04]	.823
Gestation: term	0.88 [0.58, 1.34]	.553
IMD rank	1.00 [1.00, 1.00]	.104
Multiple pregnancy	0.66 [0.46, 0.96]	.029 *
Parity		
1	0.79 [0.66, 0.95]	.010 *
2	0.87 [0.60, 1.28]	.480
3+	0.85 [0.55, 1.31]	.458
Birthweight (kg)	0.97 [0.83, 1.15]	.756
Sex:female	1.13 [0.98, 1.30]	.100
Term x time-lag (weeks)	1.01 [0.94, 1.10]	.735

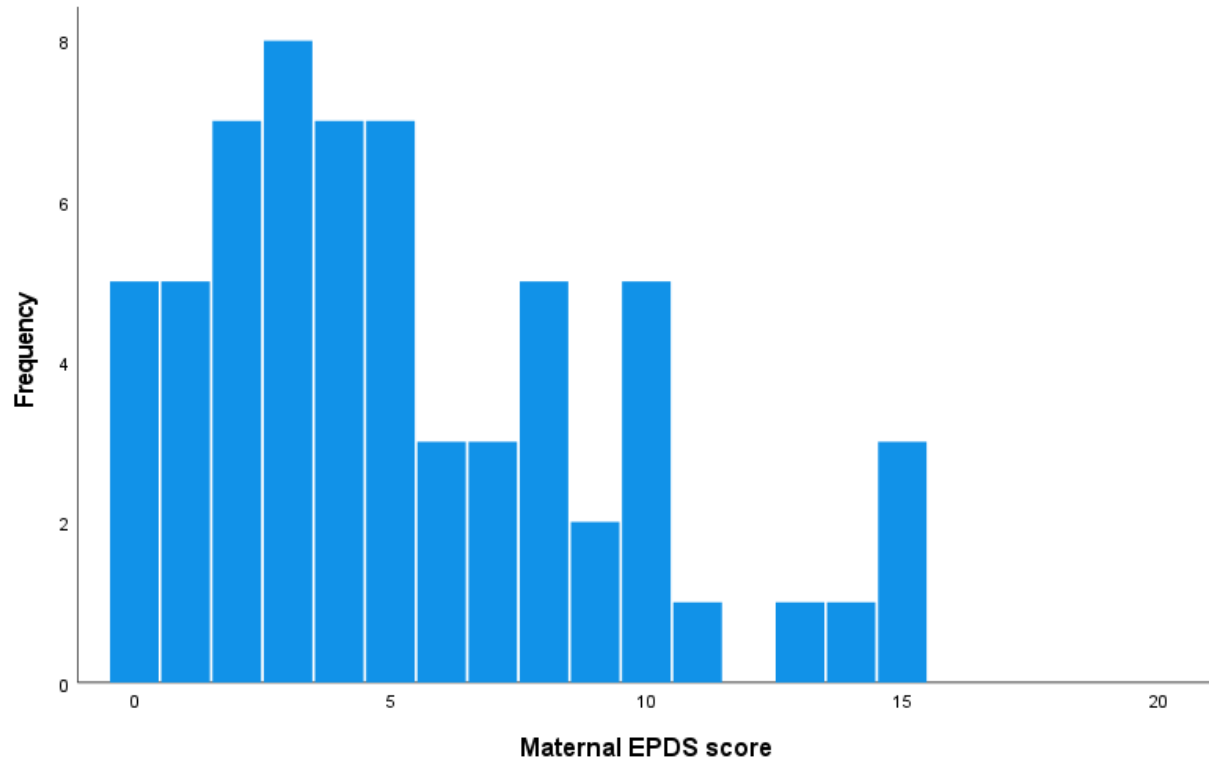
p<0.05 *; p<0.01 **; p<0.001 ***

Pseudo R² = 0.0230

IRR = incidence rate ratio

Outcome variable = maternal Edinburgh Postnatal Depression Scale (EPDS) score at term-equivalent age. Time-lag (weeks) = time in weeks between birth and EPDS assessment. Gestation: term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Term x time-lag (weeks): interaction term between term gestation at birth and time-lag between birth and maternal EPDS assessment.

Supplementary Figure 1: Histogram showing the distribution of maternal EPDS scores at term-equivalent age.



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3 **Supplemental reference list**
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- 5 1. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. L. Erlbaum Associates; 1988.
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For peer review only

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	1, 2
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	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
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
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
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, 8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	7
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, 11
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	7, 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
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, 12
2			(b) Report category boundaries when continuous variables were categorized	
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, 12
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	12
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	15, 16, 17
15				
16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 14, 17
18				
19				
20	Generalisability	21	Discuss the generalisability (external validity) of the study results	13, 14
21				
22	Other information			
23				
24	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	3
25				

*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

Postnatal maternal depressive symptoms and behavioural outcomes in term- and preterm-born toddlers: a longitudinal UK community cohort study.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058540.R3
Article Type:	Original research
Date Submitted by the Author:	05-Aug-2022
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Paediatrics
Keywords:	MENTAL HEALTH, Child & adolescent psychiatry < PSYCHIATRY, Developmental neurology & neurodisability < PAEDIATRICS, Depression & mood disorders < PSYCHIATRY, NEONATOLOGY

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3 **1 Postnatal maternal depressive symptoms and behavioural outcomes in term- and**
4 **2 preterm-born toddlers: a longitudinal UK community cohort study.**

5
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1
2
3 35 **Abstract**

4 36 **Objectives:** To examine the association between maternal depressive symptoms in the
5 37 immediate postnatal period and offspring's behavioural outcomes in a large cohort of term-
6 38 and preterm-born toddlers.

7 39 **Design and Participants:** Data were drawn from the Developing Human Connectome
8 40 Project. Maternal postnatal depressive symptoms were assessed at term-equivalent age, and
9 41 children's outcomes were evaluated at a median corrected age of 18.4 months (range 17.3 –
10 42 24.3).

11 43 **Exposure and outcomes:** Preterm birth was defined as <37 weeks completed gestation.
12 44 Maternal depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale
13 45 (EPDS). Toddlers' outcome measures were parent-rated Child Behaviour Checklist 1^{1/2}-5
14 46 Total (CBCL) and Quantitative Checklist for Autism in Toddlers (Q-CHAT) scores.
15 47 Toddlers' cognition was assessed with the Bayley Scales of Infant and Toddler Development
16 48 – Third Edition (Bayley-III).

17 49 **Results:** Higher maternal EPDS scores were associated with toddlers' higher CBCL (B=0.93,
18 50 95% CI 0.43-1.44, p<0.001, f²=0.05) and Q-CHAT scores (B=0.27, 95% CI 0.03-0.52,
19 51 p=.031, f²=0.01). Maternal EPDS, toddlers' CBCL and Q-CHAT scores did not differ
20 52 between preterm (n=97; 19.1% of the total sample) and term participants. Maternal EPDS
21 53 score did not disproportionately affect preterm children with respect to CBCL or Q-CHAT
22 54 scores.

23 55 **Conclusions:** Our findings indicate that children whose mothers reported increased
24 56 depressive symptoms in the early postnatal period, including subclinical symptoms, exhibit
25 57 more parent-reported behavioural problems in toddlerhood. These associations were
26 58 independent of gestational age. Further research is needed to confirm the clinical significance
27 59 of these findings.
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3 69 **Strengths and limitations of this study**
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- 5 70 • Prospective study with a large sample, using multiple imputation to reduce non-
6 response bias.
7 71
8 72 • Maternal depressive symptoms assessed as a continuous variable, providing more
9 nuanced information about the significance of subclinical symptoms.
10 73
11 74 • Maternal depressive symptoms assessed earlier than in previous studies, enabling
12 recognition of early screening opportunities for families.
13 75
14 76 • Potential common method variance bias through parent-completed child behavioural
15 assessments.
16 77
17 78 • Unknown paternal and parental factors, such as comorbid psychiatric conditions, that
18 may confound our findings.
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24 81 **Keywords**

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26 82 Postpartum Depression; Child Development; Autism; Mental Health; Child Behavior; Mood
27 Disorder; Preterm Birth.
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102 **Introduction**

103 Postnatal depression affects approximately 12% of mothers worldwide.¹ In contrast to ‘baby
104 blues’, which is a state of emotional lability that affects between 13.7%-76.0% of women in
105 the first few days after birth and typically resolves spontaneously within two weeks,²
106 postnatal depression is more severe and starts in the first few months post-partum¹. Stressful
107 life events have been linked to a heightened risk of developing postnatal depression;³ for
108 example, mothers of preterm infants have a significantly higher risk of postpartum depression
109 compared to mothers of term infants,⁴ likely due to heightened stress associated with
110 perinatal complications.⁵

111
112 Women with postnatal depression tend to be less responsive to their baby’s needs and to
113 display less affection.⁶ Therefore, in the short-term postpartum depression may affect mother-
114 infant interactions⁷ and in the long-term it may lead to alterations in brain development,⁸
115 emotional difficulties,⁹ less secure attachment, cognitive and behavioural problems in
116 childhood, and a possible increased risk of autism spectrum disorder (ASD).^{10,11} Large cohort
117 studies, such as the Avon Longitudinal Study of Parents and Children (ALSPAC), have
118 shown that these associations are even evident when maternal depression is measured on a
119 continuum of symptoms rather than a dichotomous diagnosis,¹²⁻¹⁴ supporting the notion that
120 elevated sub-diagnostic psychiatric symptoms can also negatively impact on children’s
121 development.¹⁵

122
123 Studies investigating the underlying causes that may link maternal postnatal depression to
124 child outcomes have implicated several biological and environmental variables. For instance,
125 genetic and epigenetic factors have been shown to both mediate and mitigate the
126 intergenerational transmission of psychiatric disorders,¹⁶ while lower quality parenting,
127 interparental conflict, and socioeconomic deprivation have been shown to exacerbate
128 children’s developmental risk of emotional and behavioural problems.¹¹ In addition, being
129 born preterm (i.e. <37 weeks’ gestation, as per the World Health Organization definition¹⁷)
130 has been associated with alterations in early brain development,¹⁸ as well as neurological,
131 behavioural and cognitive problems in childhood and beyond.^{19,20} Therefore, it is complex to
132 disentangle the possible effects of postnatal maternal mental health and those of perinatal
133 clinical factors on specific outcomes in preterm children, as these may involve both maternal
134 psychosocial and biological variables, as well as child preterm-related neurodevelopmental
135 morbidity.

136

137 Furthermore, a question that remains unanswered is whether preterm birth accentuates the
138 association between maternal postnatal depression and child outcome. Two theoretical
139 frameworks exist that hypothesise certain infants may be influenced differently by external
140 stimuli: the diathesis stress model proposes that certain vulnerability factors make affected
141 infants more prone to suboptimal environmental influences with subsequent poorer
142 outcomes,^{21,22} whereas the differential susceptibility model frames such factors as plasticity-
143 mediating, thus leading to poorer outcomes in negative environments, as well as better
144 outcomes in supportive environments.^{22,23} Previous studies investigating differential
145 susceptibility have shown mixed findings studying a range of environmental and clinical
146 exposures,^{24,25} with child outcomes including attachment, internalising and externalising
147 behaviour, and academic competence.²⁵ Both low birthweight in term infants (small for
148 gestational age, SGA)²⁶ and preterm birth (PTB)^{23,24,27} have been explored as distinct
149 potential susceptibility factors. This distinction is based on the different pathophysiological
150 processes underlying the respective conditions of SGA and PTB, both, or a combination, of
151 which can cause low birthweight.²⁸ For example, SGA is a marker of intra-uterine growth
152 restriction related to placental dysfunction,²⁹ whereas PTB can be caused by a multitude of
153 factors, including infection and inflammation.³⁰

154

155 Given that mothers of preterm children experience elevated levels of distress,³¹ are at high
156 risk of developing postnatal depression,³² and that preterm children themselves are vulnerable
157 to psychiatric sequelae,³³ in addition to investigating the association between very early
158 maternal postnatal depressive symptoms and child behavioural and emotional outcomes, we
159 further aimed to investigate the interaction between preterm birth and maternal depressive
160 symptoms on child outcomes. Previous work focusing on the differential susceptibility of
161 preterm born children to various environmental stimuli, as described above, had not yet
162 studied maternal depressive symptoms as a proposed exposure. We specifically aimed to
163 investigate the continuum of maternal depressive symptoms rather than solely focussing on
164 clinically significant maternal depression, so as to provide more nuanced information about
165 the importance of subclinical depressive symptoms on child outcomes. We hypothesised that
166 early postnatal maternal depressive symptoms would be more elevated in mothers of preterm
167 compared to term infants and that these would impact preterm children's behavioural and
168 emotional outcomes to a greater degree than their term counterparts.

169

170 **Methods**

171 **Sample**

172 Participants were enrolled in the Developing Human Connectome Project (DHCP,
173 <http://www.developingconnectome.org/>), a neuroimaging-focused project, with eligibility
174 criteria including pregnant women (aged ≥ 16 years) with a gestational age of 20–42 weeks,
175 and newborn infants aged 24–44 weeks; infants enrolled in the DHCP had magnetic
176 resonance imaging (MRI) at term-equivalent age. Exclusion criteria for the DHCP included:
177 contraindications to MRI, babies being too unwell to tolerate a scan, and language difficulties
178 preventing informed consent.³⁴ Toddlers were invited to the Centre for the Developing Brain,
179 St Thomas' Hospital, London, for neurodevelopmental assessment at 18 months post-
180 expected delivery date; appointments were made according to family availability as close as
181 possible to this time-point. Inclusion criteria for our follow-up study were: mother and baby
182 attendance for MRI at term-equivalent age; completed toddler neurodevelopmental
183 assessment. These inclusion criteria were met by 509 toddlers by the date of closure for this
184 analysis (26/02/2020). Of the 509 toddlers, 51 were one of a twin pregnancy, and three were
185 one of a triplet pregnancy; the sample contained 22 sibling pairs and one set of triplets. This
186 study was approved by the UK National Research Ethics Authority (14/LO/1169) and
187 conducted in accordance with the World Medical Association's Code of Ethics (Declaration
188 of Helsinki). Written informed consent was given by children's carer(s) at recruitment into
189 the study.

191 **Maternal variables**

192 Maternal age, parity, Body Mass Index (BMI), ethnicity and postcode were collected at
193 enrolment into the DHCP study. Our sample was ethnically representative of the surrounding
194 geographical area. Parity was coded as 0, 1, 2, or ≥ 3 previous children. Index of Multiple
195 Deprivation (IMD) rank was computed from the current maternal postcode using the 2019
196 IMD classification; it combines locality-specific information about income, employment,
197 education, health, crime, housing and living environment, thus providing a proxy for family
198 socioeconomic status.³⁵ Lower IMD rank corresponds to greater social deprivation. Our
199 sample was generally less deprived than the surrounding geographical areas, as well as the
200 UK as a whole, reflecting trends observed in other UK longitudinal studies.³⁶

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202 *Maternal depressive symptoms* were measured using the Edinburgh Postnatal Depression
203 Scale (EPDS)³⁷ on the day of infant's MRI at term-equivalent age. Mothers of infants born at

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3 204 term were tested in the first few weeks postnatally, whereas mothers of preterm-born infants
4 205 were tested once they reached term-corrected age. The EPDS is a 10-item screening
5 206 questionnaire completed by mothers, with higher scores reflecting a higher likelihood of
6 207 depressive disorders. A score of 13 can be used as a cut-off indicating high-level symptoms,
7 208 although a cut-off of 11 maximises the sensitivity and specificity of the screening tool for
8 209 depression.³⁸ Mothers completed the EPDS independently in a private room in our Centre,
9 210 with no interaction with the researcher. Participants were informed that the results would be
10 211 discussed with them, and consented to information being shared with their General
11 212 Practitioner in the case of high scores. The EPDS questionnaire was scored by a member of
12 213 the DHCP team.³⁴
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23 Child variables

24 216 Infant *clinical characteristics* were gathered from clinical notes where available, or from
25 217 maternal report, and included: sex, gestational age at birth, birth weight, and pregnancy size
26 218 (singleton/twin/triplet).
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31 220 *Behavioural outcomes* were assessed using the Child Behaviour Checklist/1^{1/2}-5 (CBCL), a
32 221 parent-completed 100-item questionnaire, in which the parent rates the child's behaviour over
33 222 the preceding two months using a 3-point Likert scale ("not true", "somewhat or sometimes
34 223 true", and "very true or often true"). Responses are categorised into syndrome profiles, and
35 224 these are subsequently grouped into internalising (emotional reactivity, anxiety/depression,
36 225 somatic complaints, and withdrawal), externalising (attention problems, aggressive
37 226 behaviour) and total (internalising, externalising, sleep and other) problem scales. Higher
38 227 scores indicate increased emotional and behavioural problems. Total scores are classified into
39 228 a normal range (<83rd centile, T <60), borderline range (83rd-90th centile, T 60-63), and
40 229 clinical range (>90th centile, T ≥64).³⁹ The CBCL is known to have high reliability, validity
41 230 and cross-informant agreement for measuring children's emotional and behavioural
42 231 problems.³⁹
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53 233 We used the Quantitative Checklist for Autism in Toddlers (Q-CHAT) as an additional
54 234 behavioural screening tool to broaden the exploration of mental health outcomes in toddlers.
55 235 The Q-CHAT is a parent-completed 25-item questionnaire, in which the child's behaviour is
56 236 scored on a 5-point (0-4) frequency scale. Higher total scores correspond to a higher
57 237 frequency of behaviours also observed in autism spectrum conditions. The Q-CHAT shows

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3 238 good test-retest reliability, face validity and specificity, yet poor positive predictive value for
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5 239 autism,^{40,41} highlighting that higher Q-CHAT scores may reflect developmental immaturity
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7 240 rather than autism.⁴¹

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9 241
10 242 *Cognitive assessment* was performed using the Bayley Scales of Infant and Toddler
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12 243 Development – Third Edition (Bayley-III). The Bayley-III provides scores for a child's
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14 244 overall cognitive, language and motor development. The cognitive standardised composite
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16 245 score was used in this study; scores between 70-84 indicate mild cognitive impairment,
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18 246 scores between 55-69 indicate moderate impairment, and scores lower than 55 indicate severe
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20 247 impairment⁴². Reliability and validity of the Bayley-III have been shown to be robust,⁴³
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22 248 although some studies report its underestimation of developmental problems.⁴⁴

23
24 250 Assessments were carried out by staff experienced in the neurocognitive assessments of
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26 251 toddlers.

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29 253 Analysis

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31 254 Descriptive statistics and one-way ANOVA tests were performed in IBM SPSS Statistics for
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33 255 Windows v.25. All other analyses were carried out in Stata v.16.

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36 257 Multiple imputation (MI) was carried out to account for missing data in CBCL (11/509,
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38 258 2.24%), Q-CHAT (9/509, 1.8%), maternal EPDS (73/509, 14.3%), maternal BMI (27/509,
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40 259 5.3%) and IMD rank (3/509, 0.6%). Variables were imputed simultaneously using the 'mi
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42 260 impute chained' procedure that performs imputation by chained equations. The imputation
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44 261 models had the same structural form as the analysis models, and included all variables that
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46 262 appear in the corresponding analysis models (maternal EPDS, maternal BMI, multiple
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48 263 pregnancy, parity, IMD rank, gestational age at birth, birthweight, sex, corrected age at
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50 264 assessment, and Bayley III Cognitive Composite score). In the imputation models we also
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52 265 included variables that were associated with the incomplete variables at the 20% level. As
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54 266 such, maternal age was included in the imputation model because it was found to be a
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56 267 significant predictor of the total CBCL raw score (p=0.001), the Q-CHAT score (p=0.021)
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58 268 and EPDS score (p=0.122) when it was included as an independent variable in regression
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60 269 models.

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3 271 Maternal EPDS and CBCL were imputed using Poisson regression; Q-CHAT, maternal BMI,
4 272 and the IMD rank were imputed using linear regression. 40 MI datasets were created. To
5 273 assess the stability of our MI parameters, we extracted the Monte Carlo error of each
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7 274 parameter estimate and examined whether the error for the coefficient was less than 10% of
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9 275 the parameter's standard error estimate. MI estimates were used for the primary analyses and
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11 276 compared to the estimates from complete-case (CC, individuals who had no missing data pre-
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13 277 imputation) analyses. Conditional normality was inspected in the complete-case analyses
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15 278 using QQ plots of the residuals of the models. Sensitivity analyses with and without extreme
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17 279 values were conducted. Initially, we fit the model using all available data, constructed the
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19 280 residuals and examined the QQ plot. Extreme values were then removed, models re-fitted
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21 281 without these values, and new QQ plots of residuals constructed again to check for any new
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23 282 extreme values. This process was repeated as many times as needed to remove all extreme
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25 283 values. During this process, the resulting estimates from the models were being examined as
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27 284 to whether they had substantially changed. We found that the removal of extreme values did
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29 285 not make any difference to the estimated parameters, and hence present the results from the
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31 286 full sample.

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33 287
34 288 The analysis models were multiple linear regressions fitted using the 'mi estimate' procedure,
35 289 which estimates effects after application of Rubin's rules.⁴⁵ To account for the small amount
36 290 of clustering in our data (twin/triplet siblings), the models' standard errors were obtained
37 291 using Stata's robust cluster estimator 'vce(cluster *idvar*)'. For continuous variables, Cohen's
38 292 f-squared effect sizes were calculated using $f^2 = (R_{AB}^2 - R_A^2)/(1 - R_{AB}^2)$, where R_{AB}^2 is the R-
39 293 squared value from a regression model that includes the variable of interest as well as all the
40 294 covariates used in the model, and R_A^2 is the R-squared value from the regression model that
41 295 includes only the covariates.^{46,47} For binary variables, Cohen's f-squared effect sizes were
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43 296 produced after estimating first the Cohen's d using the formula: $f^2 = \frac{d}{2k}$, where k is the
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45 297 number of groups. As a measure of dispersion, Cohen's d used the average root mean-square
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47 298 error over the MI datasets. Adjusted R-squared values after MI were extracted after
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49 299 estimating the model with the user-written 'mibeta' command with the 'fisherz' option,⁴⁸
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51 300 which calculates R-squared measures for linear regression with MI data. The significance of
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53 301 the joint effect of the categorical variable parity was assessed using 'mi test' which performs
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55 302 Wald tests of composite linear hypotheses.

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3 304 *Primary outcome measures* were children's total CBCL raw score and Q-CHAT score.
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5 305 *Secondary outcome measures* were CBCL internalising and externalising scores. The effect
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7 306 of maternal EPDS score was adjusted for IMD rank, maternal age, maternal BMI, maternal
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9 307 parity, pregnancy size, and the following child's variables: continuous gestational age, birth
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11 308 weight, Bayley-III cognitive composite score, and corrected age at assessment. The
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13 309 interaction between preterm birth and maternal depressive symptoms was explored using a
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15 310 complete case analysis in both CBCL and Q-CHAT models, using a dichotomised measure of
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17 311 gestational age. EPDS, CBCL and Q-CHAT scores were compared between term (≥ 37 weeks
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19 312 gestation) and preterm infants (< 37 weeks gestation) using the complete case dataset. Our
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21 313 regressions were thus run twice: with and without the interaction term.
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25 315 As all mothers had their EPDS score measured near term (or term-corrected in the case of
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27 316 mothers of preterm infants), we further investigated the association between time elapsing
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29 317 between baby's birth and mother's EPDS assessment and EPDS score, in order to avoid
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31 318 erroneously identifying 'baby blues' in mothers of term-born infants versus postnatal
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33 319 depression in mothers of preterm infants. This post-hoc analysis was performed using
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35 320 Poisson regression.
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322 Patient and Public Involvement

36 323 The current study was developed in consultation with the Weston Programme for Family
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38 324 Centered Research, which involves parents to define what research is valuable to them, and to
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40 325 allow them to lead it with support from the scientists in the Centre for the Developing Brain.
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42 326

43 **Results**

44 Descriptive statistics

45 328 Our sample of 509 toddlers were followed up at a median corrected age of 18.4 months
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47 329 (range 17.3 – 24.3 months). 51 (10.0%) of these were twins, and 3 (0.59%) were triplets. Of
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49 330 the 509, 21 (4.13%) mothers scored above a clinical cut-off (≥ 13) on the EPDS; (26) the
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51 331 distribution of maternal EPDS scores is shown graphically in Supplementary Figure 1.
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53 332 Demographic data are shown in Table 1. Complete data were available for 400 (78.6%)
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55 333 participants. Missing data were imputed and thus all 509 subjects were included in the
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57 334 primary and secondary analyses. One participant was excluded from the cognition analysis
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59 335 after examining the quintiles of the residuals against the theoretical quintiles of a normal
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336 distribution. The mean CBCL T score was 46.9 (SD 9.5) (Table 1); using CBCL-specified
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3 338 cut-offs,³⁹ 449 (90.2%) of participants had a CBCL score in the normal range, 30 (6.0%)
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5 339 were borderline, and 19 (3.8%) scored in the clinical range. The mean Q-CHAT score was
6
7 340 30.5 (SD 9.3) (Table 1). The mean Bayley III Cognitive Composite score in our sample was
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9 341 100 (SD 11.4) (Table 1), which corresponds to the standardised test mean;⁴² 480 (94.3%) of
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11 342 participants had a normal cognitive score, 24 (4.7%) had mild impairment, 5 (1%) had
12
13 343 moderate impairment, and nil had severe impairment. This distribution is not dissimilar from
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15 344 that of the normative sample.⁴²

15 345

17 346 Association between maternal EPDS score and toddler CBCL and Q-CHAT scores

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19 347 Predictors of children's CBCL and Q-CHAT scores after multiple imputation are shown in
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21 348 Table 2. Higher maternal EPDS score was associated with children's higher CBCL Total
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23 349 score (B=0.93, 95% CI 0.43-1.44, p<0.001, f²=0.05) and Q-CHAT score (B=0.27, 95% CI
24
25 350 0.03-0.52, p=.031, f²=0.01) (Table 2). These associations are presented graphically in Figure
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27 351 1 and Figure 2, respectively. Boys had higher CBCL and Q-CHAT scores than girls. Higher
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29 352 Q-CHAT scores were associated with lower IMD rank (i.e., greater socio-economic
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31 353 deprivation) and lower Bayley-III cognitive composite scores. Parity was not a significant
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33 354 predictor of outcome in any of the models (Table 2).

33 355

34 356 Maternal EPDS score did not disproportionately affect preterm children with respect to
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36 357 CBCL or Q-CHAT scores (Table 3).

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39 359 Association between maternal EPDS score and toddler CBCL internalising and externalising scores

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43 361 Higher maternal EPDS score was associated with both internalising (B=0.22, 95% CI 0.08-
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45 362 0.36, p<0.01, f²=0.03) and externalising (B=0.40, 95% CI 0.20-0.61, p<0.001, f²=0.05)
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47 363 symptoms in children (Supplementary Table 1 and 2, respectively). Comparison of the
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49 364 imputed model analyses to the complete-case analyses showed that results were consistent for
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51 365 the CBCL model (Supplementary Table 3). Comparison for the Q-CHAT model showed that
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53 366 maternal EPDS was a significant predictor in the imputed model, but not in the complete-case
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55 367 analysis (Supplementary Table 3).

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57 369 Effect of time-lag between baby's birth and mother's EPDS assessment and EPDS score

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59 370 Mothers who gave birth prematurely (<37 weeks gestation) had their EPDS score assessed on
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371 average 7.7 weeks later post-delivery than mothers who gave birth at term (preterm

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3 372 participants $M=8.9$ (SD 4.8), term participants $M=1.2$ (SD 1.3); $t(99.4)=15.5$, $p<.001$). The
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5 373 time-lag between birth and EPDS assessment did not predict maternal EPDS score, and there
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7 374 was no evidence of a significant interaction between gestation and birth-to-assessment time-
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9 375 lag (Supplementary Table 4 and 5, respectively).

376

377 **Discussion**

378 **Principal findings**

379 Our results showed that more maternal self-reported depressive symptoms shortly after birth
380 were associated with greater parent-reported toddlers' behavioural problems. Given that
381 fewer than 5% of the mothers in our cohort had EPDS scores above a clinical threshold,³⁷ our
382 findings indicate that even subclinical depressive symptoms – i.e. not only diagnostic
383 postnatal depression – adversely impact children's behavioural outcomes. In addition, our
384 cohort was typically developing with few CBCL scores reaching a concerning threshold; our
385 results could be interpreted within the conceptual framework of mental illness lying on a
386 continuum with typical behavioural traits.⁴⁹ Our findings further showed that preterm birth
387 did not influence the association between self-reported maternal depressive symptoms and
388 parent-reported infants' behavioural outcomes in toddlerhood. This indicates that in this
389 context preterm birth may not be regarded as a vulnerability or plasticity factor. Interestingly,
390 mothers of preterm infants did not report more depressive symptoms compared to mothers of
391 term infants in this study.

392

393 **Comparison to prior literature**

394 Our results with respect to internalising and externalising symptoms are in line with previous
395 studies, including large population cohort studies, that showed an association between
396 postnatal maternal depression and young children's emotional and behavioural problems.¹¹
397 Another previous study in 18-month old toddlers found that maternal depression was
398 associated with internalising and dysregulated behaviour, but not externalising symptoms.⁵⁰
399 This difference between our and Conroy et al.'s findings may have arisen from their
400 exclusion of infants born <36 weeks and their use of a clinical diagnosis of depression for
401 mothers, rather than the continuous self-reported approach we employed. Interestingly, our
402 finding that even subclinical depressive symptoms may adversely impact parent-reported
403 child behavioural outcomes is in line with recent data showing that low- as well as high-level
404 depressive symptoms are associated with internalising and externalising symptoms in
405 children aged 3 years.⁵¹

406

The results showing an association between maternal postnatal depressive symptoms and the Q-CHAT are less robust and need to be interpreted with caution. Firstly, these results must be viewed in the context of the Q-CHAT having a low positive predictive value for autism, with the measure perhaps being more reflective of developmental immaturity.⁴¹ Although some prior studies have shown an association between antenatal maternal depression and offspring's ASD,^{10,52} and postnatal depression has been suggested as a potential focus of cross-domain studies of ASD,⁵³ there is no clear aetiological role of maternal postnatal depression in the development of ASD *per se*. Also, given that mothers with ASD are more likely to suffer from perinatal depression than mothers without ASD,⁵⁴ and ASD is highly heritable,⁵⁵ maternal depression may actually be a confounding rather than causative factor in our observed results. Overall, therefore, our findings with respect to the Q-CHAT do not provide support for a role of maternal depression in the aetiology of autism traits, but rather suggest that maternal depression can influence toddler behaviour.

420

The finding that preterm infants were not disproportionately affected by maternal depressive symptoms supports Hadfield et al.'s findings that maternal distress at 9 months did not differentially impact very preterm (<34 weeks) or late preterm (34-36⁺⁶ weeks) infants with respect to socioemotional outcomes, although paternal distress did have an impact on very preterm infants' outcomes.²⁴ However, our results differ from Gueron-Sela et al.'s finding that very preterm (28-33 weeks) 12 month old infants' social outcomes were more influenced by maternal emotional distress at 6 months than term infants' outcomes.²³ The inconsistent findings may be due to methodological differences: for instance, our infant assessment being conducted at 18 months corrected age when social competency is more developed, our assessment of maternal depressive symptoms being in the very early postnatal period, or our use of the CBCL and Q-CHAT tools as markers of toddler behaviour. Importantly, the lack of support for a diathesis-stress or differential susceptibility model of maternal mental state on preterm infants in our study must be viewed in the context of our results also showing no difference in CBCL and Q-CHAT scores between term and preterm infants. This is in contrast to the existing literature that preterm infants are more likely than term infants to develop behavioural problems, such as ADHD, in childhood and adolescence.^{20,33} It is possible that the phenotypes of neurodevelopmental and neuropsychiatric disorders assessed with the chosen behavioural measures may not be sufficiently expressed at 18 months

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3 439 corrected age.⁵⁶ In addition, as briefly discussed above, much of the existing literature
4 440 emphasises the risk of extreme (<28 weeks) or very preterm (28-33 weeks) birth on later
5 441 behavioural outcomes,^{20,33} whereas only 3.5% and 5.5% of our participants fell within the
6 442 extreme and very preterm group, respectively, and we thus may not have the power to show
7 443 any subtle effects.
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11 444 12 13 **Strengths & limitations of the study** 14

15 446 The strengths of this study lie primarily in its large sample and prospective data collection.
16 447 Moreover, the use of multiple imputation methodology has facilitated retention of a complete
17 448 dataset, thus minimising non-response bias and increasing parameter precision. A strength in
18 449 comparison to prior population cohort studies is that we assessed very early maternal
19 450 depressive symptoms, and our sample is perhaps more representative of today's society –
20 451 with increasing maternal age – than large cohort studies conducted in the 1990s-2000s. Given
21 452 the complex interplay of biological and environmental factors in the aetiology of behavioural
22 453 disorders, the inclusion of a substantive proportion of preterm infants in our cohort also offers
23 454 an important insight into the role of preterm birth in behavioural outcomes; moreover, our
24 455 results represent the full gestational spectrum, rather than discrete gestational categories. In
25 456 addition, using maternal depressive symptoms as a continuous, rather than dichotomous,
26 457 variable allows a more nuanced understanding of the role maternal postnatal depressive
27 458 symptoms may play in influencing children's outcomes.
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39 460 There are several limitations to this study that necessitate our findings to be considered with
40 461 caution. Firstly, differences in birth-to-EPDS-assessment time-lags are a potential
41 462 confounder, given the time-sensitive nature of early-onset temporary baby blues and later-
42 463 onset pathological postnatal depression. Mothers of infants born at term were assessed early
43 464 post-delivery, within the period one would anticipate baby blues to present, whereas mothers
44 465 of preterm participants were on average assessed later, when postnatal depression
45 466 predominates.^{1,57} Although our post-hoc analyses showed that the time elapsed from birth to
46 467 EPDS assessment was not associated with maternal EPDS score, providing reassurance that
47 468 our assessments of mothers of term-born infants were not inflated by the common temporary
48 469 symptoms of baby blues, it is possible that we did not capture the full extent of later-onset
49 470 depressive symptoms in mothers of term-born infants. This may explain why maternal EPDS
50 471 scores did not differ between preterm and term groups in our complete dataset analysis,
51 472 contrary to the current literature,³¹ as well as why our rate of postpartum depression, using an

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3 473 EPDS cut-off of 13, was low (4.1%) compared to the previously documented UK community
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5 474 prevalence rate of 8.9% at eight weeks postpartum.⁵⁸ Our results must therefore be
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7 475 interpreted with some caution.
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9 476

10 477 Secondly, although statistical techniques were used to impute missing data and mitigate this
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12 478 problem, 14.3% of maternal EPDS scores were missing. This rate of missingness may relate
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14 479 to some mothers being reluctant to complete a questionnaire at the time their child is having
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16 480 an MRI, or due to simultaneous childcare duties. Thirdly, a number of important confounders
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18 481 that are likely to affect children's behavioural outcomes were not assessed in this study,
19
20 482 including genetic risk for psychiatric disorders,⁵⁹ parental psychiatric co-morbidities,⁵⁰
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22 483 chronicity of postnatal depressive symptoms,⁵¹ antenatal maternal depression, paternal
23
24 484 depression and subsequent parent-infant attachment, and inter-parental conflict.¹¹ Thus, we
25
26 485 are unable to conclude whether our observed associations between early postnatal maternal
27
28 486 depressive symptoms and children's behavioural outcomes are moderated or mediated by
29
30 487 other parental and/or psychiatric factors.
31
32 488

33 489 Fourthly, whilst our study included a reasonable proportion of preterm infants (97/509, 19%),
34
35 490 our sample was not random, as preterm children were selectively recruited for the DHCP;
36
37 491 indeed, preterm infants are over-represented in our sample when compared to the UK
38
39 492 population incidence (7.3%),⁶⁰ which may limit the study's generalisability to the general
40
41 493 population. This over-representation of preterm infants may explain why our mean maternal
42
43 494 age is higher than the national mean age of 30.7,⁶¹ given that increasing maternal age is
44
45 495 associated with increased risk of adverse pregnancy outcomes.⁶² Our observed large maternal
46
47 496 age range in itself also poses a limitation on the generalisability of our findings to the general
48
49 497 population, and further research would be necessary to identify a possible moderation effect
50
51 498 of high maternal age on both EPDS scores and child behavioural outcomes. Furthermore,
52
53 499 although a 19% prevalence of preterm birth is high for a community sample, the proportion
54
55 500 of very and extreme preterm infants in our sample is small, and this may not have provided
56
57 501 sufficient power to detect any differential susceptibility effect of preterm birth on outcomes.
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59 502

60 503 Sixthly, the effect sizes of the association between maternal EPDS score and behavioural
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62 504 problems were small; this raises questions regarding the clinical significance of our findings
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64 505 and potentially explains some of the inconsistency between this and previous studies. Even
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66 506 within our analyses, the association between maternal depressive symptoms and Q-CHAT

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3 507 scores was not observed in our complete case analysis, thus calling into question the validity
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5 508 of this result. It is also important to highlight again the poor positive predictive value of the
6
7 509 Q-CHAT for autism;⁴¹ higher Q-CHAT scores do not imply a diagnosis of ASD, and this
8
9 510 distinction may also explain the contrast to previous studies.

10 511
11
12 512 Finally, it is well documented that maternal depression influences reporting of Q-CHAT ⁶³
13
14 513 and CBCL scores.⁶⁴ Our study used maternal report of maternal depressive symptoms, and
15
16 514 our outcome measures were parent-completed questionnaires; despite the CBCL showing
17
18 515 good cross-informant agreement,³⁹ it is thus possible that reporting bias with common
19
20 516 method variance could have skewed our results.

21 517

22 518 **Implications of our findings**

23
24 519 Of greatest importance to clinicians and policymakers is our finding that even *subclinical*
25
26 520 self-reported maternal depressive symptoms are associated with parent-reported behavioural
27
28 521 outcomes of offspring. This has significant implications for the risk-stratification of women
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30 522 and their babies in the postnatal period, during which contact with medical professionals is
31
32 523 already established. Identifying high risk families and providing appropriate supportive
33
34 524 measures at the early postnatal stage may help to prevent future psychiatric morbidity.

35 525

36 526 **Future research**

37
38 527 Further follow-up of large cohorts of preterm and term infants, to an age when behavioural
39
40 528 phenotypes may become more pronounced, is needed to investigate whether the long-term
41
42 529 developmental trajectories of term and ex-preterm infants are differentially susceptible to
43
44 530 changes of postnatal maternal mental health. Future research should consider both maternal
45
46 531 and paternal mental health, as well as socioeconomic and environmental factors on child
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48 532 outcomes. Such follow-up should use independent, objective assessments of child
49
50 533 behavioural outcomes in order to avoid the common method variance inherent to parent-
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52 534 reported measures. Finally, it is crucial for future research to elucidate the interplay of
53
54 535 biochemical and neurodevelopmental changes that may mediate and confound the translation
55
56 536 of environmental exposures into distal behavioural phenotypes.

57 537

58 538 **Conclusion**

59 539 This prospective longitudinal cohort study found no evidence to support the concept of
60 540 preterm birth as a vulnerability or plasticity factor with respect to the effect of maternal

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3 541 depressive symptoms on behavioural development. However, we showed that early
4 542 subclinical maternal postnatal depressive symptoms were associated with behavioural
5 543 problems in children on parent-reported measures. This adds to the increasing body of
6 544 literature indicating the role of subclinical and early postnatal depressive symptoms in the
7 545 aetiology of childhood behavioural disorders. These findings are of great relevance to child
8 546 and public health, and further research may strengthen its implications for developing
9 547 strategies to facilitate effective screening and support for women and children, enabling all to
10 548 reach their full potential.
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30 557 **Investigation:** SF, AC; **Data curation:** IK, AL; **Formal analysis:** IK, GV, AP, CN;
31 558 **Writing – original draft preparation:** IK; **Writing – Review & Editing:** GV, AL, SF, AC,
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4
5 576 authors and not necessarily those of the NHS, the NIHR, or the Department of Health and
6
7 577 Social Care.
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9 578

10 579 **Conflict of interest / Competing interests**

11 580 ADE received financial support from the EU-AIMS-Trials (European Research Council
12
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14
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16
17 583 newborn infants) and Medtronix (unpaid participation in scientific advice committee). ADE
18
19 584 has a patent on Xenon as an organ protectant (No P023708WO). ADE was Chair of the Data
20
21 585 Monitoring and Ethics Committee for the Baby-Oscar Trial, and served on the Data
22
23 586 Monitoring and Ethics Committee for the PAEN Trial.
24
25 587

26 588 There are no other relationships or activities that could appear to have influenced the
27
28 589 submitted work.
29
30 590

31 591 **Ethics approval**

32 592 This study was approved by the UK National Research Ethics Authority (14/LO/1169) and
33
34 593 conducted in accordance with the World Medical Association's Code of Ethics (Declaration
35
36 594 of Helsinki).
37
38 595

39 596 **Consent to participate**

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41 597 Written informed consent was given by children's carer(s) at recruitment into the study.
42
43 598

44 599 **Consent for publication**

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46 600 Not applicable.
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48 601

49 602 **Data sharing**

50
51 603 Research data are available upon reasonable request.
52
53 604

54 605 **Code availability**

55
56 606 Not applicable.
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805 **Table 1: Socio-demographic, maternal and clinical characteristics (n=509)**

Variable	Number (%)*
Sex: Male	274 (53.8)
Index of Multiple Deprivation (IMD) quintiles	
1 (least deprived) ^a	65 (12.8)
2	87 (17.2)
3	108 (21.3)
4	173 (34.2)
5 (most deprived)	73 (14.4)
Gestational age at birth (weeks), median [range]	39.7 [20 – 43]
Gestational category	
Extremely preterm (<28 weeks)	18 (3.5)
Very preterm (28-32 weeks)	28 (5.5)
Late preterm (32-37 weeks)	51 (10.0)
Term (≥37 weeks)	412 (80.9)
Birthweight (g), median [range]	3290 [450 – 4750]
Multiple pregnancy	54 (10.6)
Maternal parity	
0	332 (65.2)
1	124 (24.4)
2	32 (6.3)
3+	21 (4.2)
Maternal BMI (kg/m ²), median [range]	23.2 [15.3 – 43.6]
Maternal age at infant's birth (years), mean (SD) [range]	34.2 (4.8) [17 – 52]
Maternal ethnicity	
White	272 (53.4)
Black/Black British	56 (11.0)
Asian/Asian British	28 (5.5)
Chinese	18 (3.5)
Mixed – White & Asian	4 (0.8)
Mixed – White & Black	4 (0.8)
Any other	30 (5.9)
Do not wish to answer	9 (1.8)
No data	88 (17.3)
Bayley III cognitive composite score, mean (SD) [range]	100 (11.4) [55 – 125]
CBCL total T score, mean (SD) [range]	46.9 (9.5) [28 – 69]
Q-CHAT total score, mean (SD) [range]	30.5 (9.3) [8 – 70]
EPDS score, median [range]	4 [0 – 28]
EPDS score, n (%)	
<13	415 (8.2)
≥13	21 (4.1)
No data	73 (14.3)

806 ^a Quintile 1 corresponds to the highest, least deprived, IMD rankings.

807 * unless otherwise specified

Table 2: CBCL and Q-CHAT model predictors using multiple imputation without interaction. (Cf. Supplementary Table 3 for complete case analysis)

	CBCL			Q-CHAT		
	B [95%CI]	p	f ²	B [95%CI]	p	f ²
Maternal EPDS	0.93 [0.43, 1.44]	<.001 ***	0.05	0.27 [0.03, 0.52]	.031 *	0.01
Maternal BMI	-0.09 [-0.44, 0.26]	.621	-	0.06 [-0.13, 0.24]	.538	-
Multiple pregnancy	3.15 [-3.07, 9.37]	.320	-	1.33 [-2.62, 5.28]	.509	-
Parity						
1	-2.52 [-5.96, 0.93]	.151	-	-2.14 [-4.02, -0.27]	.025 ^a	-
2	-3.23 [-9.16, 2.70]	.285	-	0.88 [-1.99, 3.75]	.548	-
3+	-1.37 [-8.36, 5.61]	.699	-	-0.49 [-4.57, 3.60]	.815	-
IMD rank	-1.48 [-3.33, 0.37]	.117	-	-1.50 [-2.60, -0.40]	.008 **	0.02
Gestational age at birth (weeks)	0.10 [-0.65, 0.85]	.786	-	0.26 [-0.17, 0.70]	.233	-
Birthweight (kg)	0.56 [-2.65, 3.78]	.731	-	-1.24 [-2.93, 0.46]	.151	-
Sex:female	-4.14 [-6.96, -1.31]	.004 **	0.06	-1.95 [-3.42, -0.48]	.009 **	0.05
Corrected age at assessment (months)	-0.90 [-2.17, 0.37]	.166	-	-0.16 [-0.91, 0.59]	.677	-
Cognition	-0.05 [-0.20, 0.09]	.467	-	-0.27 [-0.35, -0.20]	<.001 ***	0.12

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL model adjusted R² = 0.0676. Q-CHAT model adjusted R² = 0.193.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

^a Wald test of whole parity variable in Q-CHAT model: F(3, 476.9) = 1.88, p = .133

Effect size (Cohen’s f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.⁴⁶

- indicates data not given, as predictor not significant to 0.05.

Table 3: CBCL and Q-CHAT model predictors using complete case analysis with interaction of ‘EPDS x term’.

	CBCL		Q-CHAT	
	B [95%CI]	p	B [95%CI]	p
Maternal EPDS	0.89 [-0.24, 2.02]	.121	0.24 [-0.28, 0.75]	.365
Maternal BMI	-0.01 [-0.39, 0.37]	.955	0.00 [-0.16, 0.17]	.982
Multiple pregnancy	1.76 [-6.65, 10.17]	.681	0.97 [-2.07, 4.01]	.532
Parity				
1	-2.75 [-6.49, 0.99]	.149	-1.42 [-3.30, 0.46]	.139
2	-3.49 [-10.36, 3.37]	.317	0.16 [-2.84, 3.16]	.917
3+	-1.17 [-9.69, 7.35]	.788	-1.13 [-4.24, 1.98]	.476
IMD rank	-1.41 [-3.54, 0.73]	.195	-1.68 [-2.64, -0.72]	.001 **
Gestation: term	1.25 [-8.34, 10.85]	.797	2.64 [-1.74, 7.02]	.236
Birthweight (kg)	-1.01 [-4.08, 2.05]	.516	-2.25 [-3.73, -0.78]	.003 **
Sex: female	-4.64 [-7.83, -1.44]	.005 **	-2.22 [-3.72, -0.71]	.004 **
Corrected age at assessment (months)	-0.83 [-2.27, 0.62]	.261	-0.39 [-1.18, 0.04]	.335
Cognition	-0.03 [-0.20, 0.14]	.720	-0.22 [-0.29, -0.15]	<.001 ***
EPDS x gestation:term	-0.01 [-1.30, 1.28]	.991	-0.02 [-0.60, 0.56]	.950

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL model adjusted R² = 0.0865. Q-CHAT model adjusted R² = 0.215.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Gestation: term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth.

Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months. EPDS x gestation:term = interaction term between maternal EPDS score and term gestation at birth.

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Fig.1 Children’s predicted CBCL scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age.

Fig.2 Children’s predicted Q-CHAT scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age.

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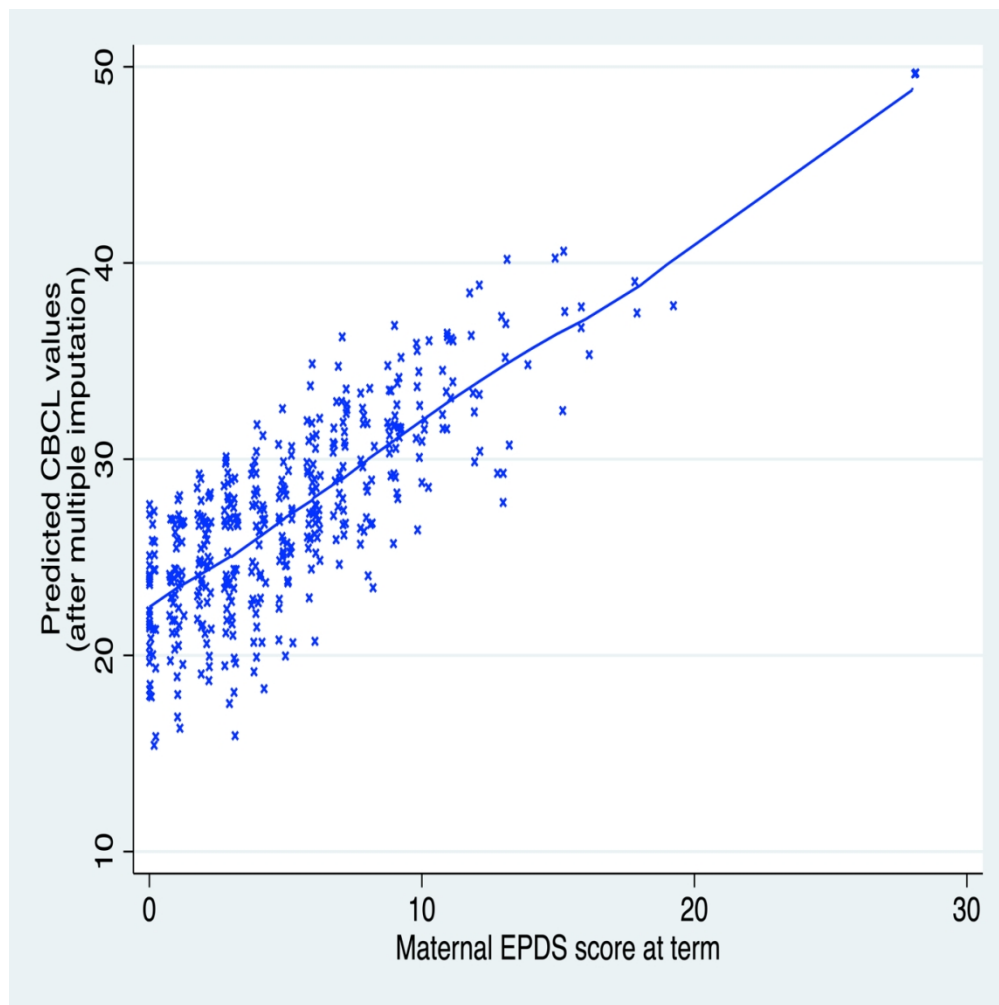


Fig.1 Children’s predicted CBCL scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age

158x158mm (220 x 220 DPI)

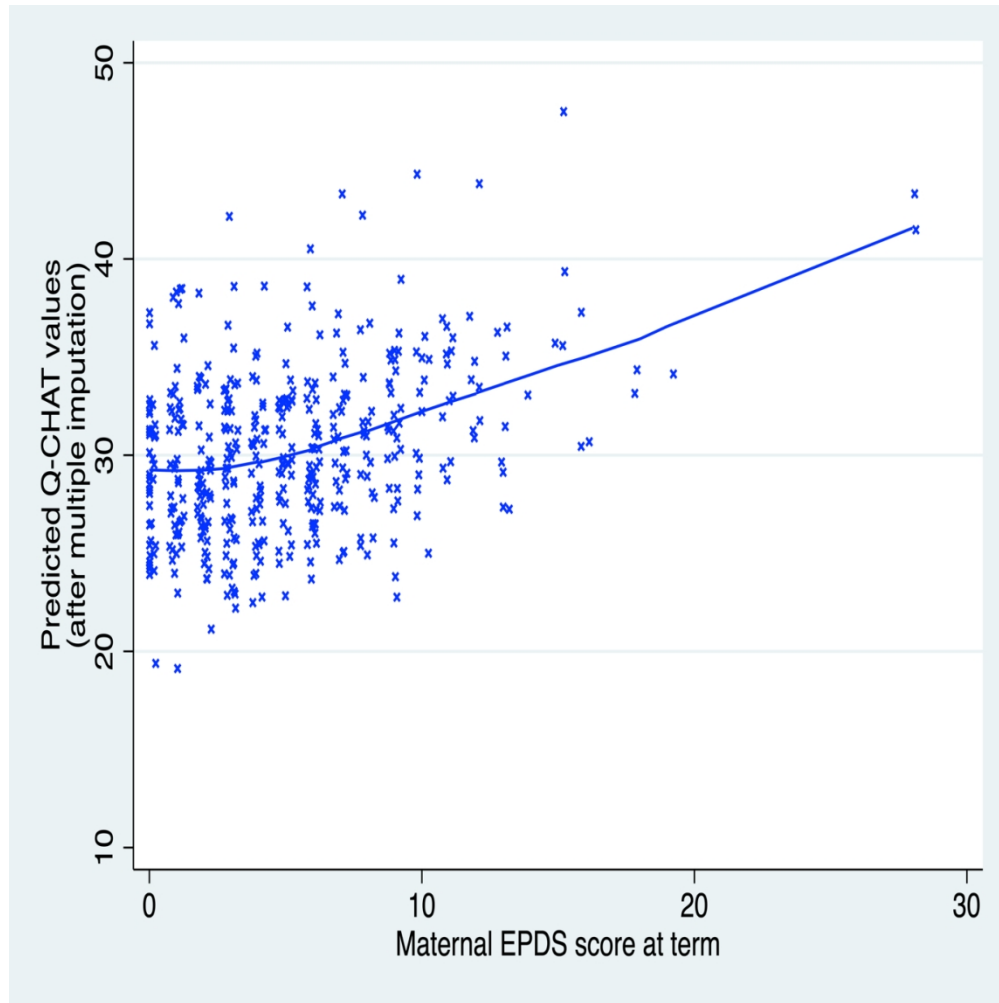


Fig.2 Children’s predicted Q-CHAT scores at 18 months are positively correlated to the maternal EPDS score at term-equivalent age.

158x158mm (220 x 220 DPI)

Supplemental material

Supplementary Table 1: CBCL internalising symptom model predictors using multiple imputation.

Supplementary Table 2: CBCL externalising symptom model predictors using multiple imputation.

Supplementary Table 3: CBCL and Q-CHAT model predictors using complete case analysis without interaction.

Supplementary Table 4: EPDS score predictors.

Supplementary Table 5: EPDS score predictors including interaction 'term x time-lag'.

Supplementary Figure 1: Histogram showing the distribution of maternal EPDS scores at term-equivalent age.

Supplementary Table 1: CBCL internalising symptom model predictors using multiple imputation.

	B [95%CI]	p	f²
Maternal EPDS	0.22 [0.08, 0.36]	.003 **	0.03
Maternal BMI	-0.04 [-0.13, 0.06]	.436	-
Multiple pregnancy	0.58 [-1.10, 2.27]	.497	-
Parity			
1	-0.37 [-1.41, 0.67]	.487	-
2	-1.33 [-3.09, 0.42]	.136	-
3+	0.64 [-1.34, 2.62]	.524	-
IMD rank	-0.41 [-0.91, 0.10]	.115	-
Gestational age at birth (weeks)	0.22 [-0.00, 0.44]	.053	-
Birthweight (kg)	-0.97 [-1.90, -0.05]	.038 *	0.005
Sex: female	-0.51 [-1.35, 0.33]	.232	-
Corrected age at assessment (months)	0.02 [-0.41, 0.45]	.923	-
Cognition	-0.05 [-0.10, -0.01]	.016 *	0.01

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.0566.

B = unstandardised coefficient.

Outcome variable = Child Behaviour Checklist internalising sub-score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.¹

- indicates data not given, as predictor not significant to 0.05.

Supplementary Table 2: CBCL externalising symptom model predictors using multiple imputation.

	B [95%CI]	p	f²
Maternal EPDS	0.40 [0.20, 0.61]	<.001 ***	0.05
Maternal BMI	0.01 [-0.17, 0.15]	.933	-
Multiple pregnancy	2.51 [-0.29, 5.31]	.079	-
Parity			
1	-1.06 [-2.53, 0.42]	.160	-
2	-0.61 [-3.55, 2.33]	.682	-
3+	-0.96 [-4.47, 2.56]	.593	-
IMD rank	-0.24 [-1.11, 0.63]	.585	-
Gestational age at birth (weeks)	-0.07 [-0.40, 0.27]	.701	-
Birthweight (kg)	1.03 [-0.38, 2.44]	.153	-
Sex: female	-1.80 [-3.07, -0.53]	.006 **	0.06
Corrected age at assessment (months)	-0.40 [-0.95, 0.16]	.161	-
Cognition	0.03 [-0.03, 0.10]	.322	-

p<0.05 *; p<0.01 **; p<0.001 ***

Adjusted R² = 0.0612.

B = unstandardised coefficient.

Outcome variable = Child Behaviour Checklist externalising sub-score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal

Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age.

Cognition = infant Bayley III score at 18 months.

Effect size (Cohen's f², calculated from squared part correlations for predictors significant to 0.05): 0.02 = small, 0.15 = medium and 0.35 = large.¹

- indicates data not given, as predictor not significant to 0.05.

Supplementary Table 3: CBCL and Q-CHAT model predictors using complete case analysis without interaction.

	CBCL		Q-CHAT	
	B [95%CI]	p	B [95%CI]	p
Maternal EPDS	0.88 [0.35, 1.41]	.001 **	0.21 [-0.02, 0.44]	.069
Maternal BMI	-0.01 [-0.38, 0.37]	.963	0.01 [-0.16, 0.17]	.930
Multiple pregnancy	1.50 [-6.87, 9.87]	.724	0.43 [-2.50, 3.37]	.772
Parity				
1	-2.83 [-6.60, 0.94]	.141	-1.54 [-3.41, 0.34]	.108
2	-3.49 [-10.3, 3.35]	.316	0.13 [-2.85, 3.10]	.933
3+	-1.38 [-10.0, 7.30]	.755	-1.43 [-4.50, 1.64]	.360
IMD rank	-1.44 [-3.56, 0.67]	.181	-1.75 [-2.70, -0.79]	<.001 ***
Gestational age at birth (weeks)	0.01 [-0.90, 0.91]	.987	0.10 [-0.33, 0.54]	.639
Birthweight (kg)	-0.65 [-4.38, 3.08]	.733	-1.81 [-3.63, 0.00]	.050
Sex: female	-4.57 [-7.82, -1.31]	.006 **	-2.12 [-3.60, -0.64]	.005 **
Corrected age at assessment (months)	-0.84 [-2.26, 0.59]	.247	-0.41 [-1.18, 0.35]	.290
Cognition	-0.03 [-0.20, 0.13]	.689	-0.23 [-0.30, -0.15]	<.001 ***

p<0.05 *; p<0.01 **; p<0.001 ***

CBCL adjusted $R^2 = 0.0862$. Q-CHAT adjusted $R^2 = 0.2103$.

B = unstandardised coefficient.

CBCL = Child Behaviour Checklist externalising sub-score at 18 months. Q-CHAT = Quantitative Checklist for Autism in Toddlers score at 18 months. Maternal EPDS = maternal Edinburgh Postnatal Depression Scale score at term-equivalent age. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Gestation (weeks) = dummy variable: 34-36+6 weeks and ≥ 37 weeks gestation at birth. Corrected age at assessment (months) = age at behavioural assessment, corrected for gestational age. Cognition = infant Bayley III score at 18 months.

Supplementary Table 4: EPDS score predictors.

	IRR [95%CI]	p
Time-lag (weeks)	1.01 [0.97, 1.05]	.647
Gestation:term	0.91 [0.64, 1.31]	.627
IMD rank	1.00 [1.00, 1.00]	.103
Multiple pregnancy	0.66 [0.46, 0.96]	.031 *
Parity		
1	0.79 [0.66, 0.95]	.011 *
2	0.87 [0.60, 1.28]	.491
3+	0.84 [0.54, 1.31]	.445
Birthweight (kg)	0.98 [0.83, 1.17]	.847
Sex:female	1.13 [0.98, 1.31]	.098

p<0.05 *; p<0.01 **; p<0.001 ***

Pseudo R² = 0.0228

IRR = incidence rate ratio

Outcome variable = maternal Edinburgh Postnatal Depression Scale (EPDS) score at term-equivalent age. Time-lag (weeks) = time in weeks between birth and EPDS assessment. Gestation:term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren).

Supplementary Table 5: EPDS score predictors including interaction ‘term x time-lag’.

	IRR [95%CI]	p
Time-lag (weeks)	1.00 [0.97, 1.04]	.823
Gestation: term	0.88 [0.58, 1.34]	.553
IMD rank	1.00 [1.00, 1.00]	.104
Multiple pregnancy	0.66 [0.46, 0.96]	.029 *
Parity		
1	0.79 [0.66, 0.95]	.010 *
2	0.87 [0.60, 1.28]	.480
3+	0.85 [0.55, 1.31]	.458
Birthweight (kg)	0.97 [0.83, 1.15]	.756
Sex:female	1.13 [0.98, 1.30]	.100
Term x time-lag (weeks)	1.01 [0.94, 1.10]	.735

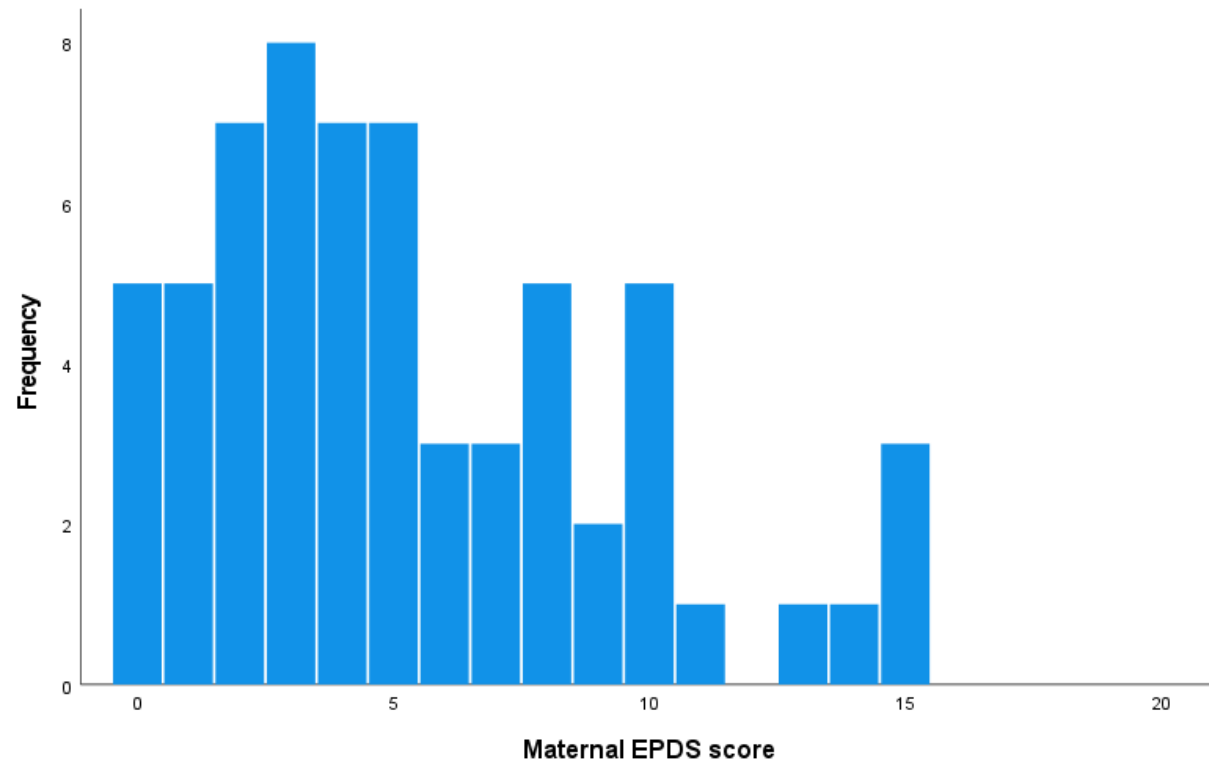
p<0.05 *; p<0.01 **; p<0.001 ***

Pseudo R² = 0.0230

IRR = incidence rate ratio

Outcome variable = maternal Edinburgh Postnatal Depression Scale (EPDS) score at term-equivalent age. Time-lag (weeks) = time in weeks between birth and EPDS assessment. Gestation: term = dummy variable, term (≥37 weeks) vs preterm (<37 weeks) gestation at birth. Multiple pregnancy = dummy variable of twin/triplet pregnancy. Parity = dummy variable, one/two/three+ previous child(ren). Term x time-lag (weeks): interaction term between term gestation at birth and time-lag between birth and maternal EPDS assessment.

Supplementary Figure 1: Histogram showing the distribution of maternal EPDS scores at term-equivalent age.



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3 **Supplemental reference list**
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- 5 1. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. L. Erlbaum Associates; 1988.
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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	1, 2
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	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
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
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
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, 8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	7
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, 11
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	7, 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
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, 12
2			(b) Report category boundaries when continuous variables were categorized	
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, 12
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	12
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	15, 16, 17
15				
16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 14, 17
18				
19				
20	Generalisability	21	Discuss the generalisability (external validity) of the study results	13, 14
21				
22	Other information			
23				
24	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	3
25				

*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>.