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The timing of maternal depressive symptoms and child cognitive development: a longitudinal study

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Background: Maternal depression is known to be associated with impairments in child cognitive development, although the effect of timing of exposure to maternal depression is unclear. **Methods:** Data collected for the Avon Longitudinal Study of Parents and Children, a longitudinal study beginning in pregnancy, included self-report measures of maternal depression the Edinburgh Postnatal Depression Scale, completed on 6 occasions up to 3 years of age, and IQ of the index child (WISC) measured at aged 8 years. We used these data to assign women to 8 groups according to whether depression occurred in the antenatal, postnatal, preschool period, any combination of these times, or not at all. We compared a model comprising all patterns of depression (saturated model) with models nested within this to test whether there is a relationship between depression and child cognitive development and, if so, whether there is a sensitive period. We then investigated the relationship with child IQ for each model, following adjustment for confounders. **Results:** Six thousand seven hundred and thirty-five of 13,615 children from singleton births (49.5%, of eligible core sample) attended a research clinic at 8 years and completed a WISC with a score ≥ 70. A total of 5,029 mothers of these children had completed mood assessments over the 3 time periods. In unadjusted analyses, all three sensitive period models were as good as the saturated model, as was an accumulation model. Of the sensitive period models, only that for antenatal exposure was a consistently better fit than the accumulation model. After multiple imputation for missing data (to n = 6,735), there was no effect of postnatal depression on child IQ independent of depression at other times [−0.19 IQ points, 95% confidence interval (CI) −1.5 to 1.1 points]. There was an effect of antenatal depression (−3.19 IQ points, 95% CI: −4.33 to −2.06) which attenuated following adjustment (−0.64 IQ points, 95% CI: −1.68 to 0.40). **Conclusions:** The postnatal period is not a sensitive one for the effect of maternal depression on child cognitive development. **Keywords:** Perinatal, maternal depression, child development, depression, intelligence.

Background

The early environment has an important influence on cognitive development. Numerous animal studies have shown that early deprivation, particularly maternal separation (Enthoven, de Kloet, & Oitzl, 2008; Lupien, McEwen, Gunnar, & Heim, 2009) and variation in maternal care (Liu, Diorio, Day, Francis, & Meaney, 2000; Novak & Harlow, 1975) can affect brain development and thus adversely affect cognitive functioning. In these studies, the effect of early deprivation can persist with limited or no improvement when reversed at later stages (de Kloet & Oitzl, 2003), indicating that offspring may be more sensitive to the enduring effects of an adverse exposure if it occurs at a particular time in development. These studies of rodents indicate that the early postnatal environment may be particularly influential in brain development, raising the important question about whether this is true for human cognitive development. It is difficult to generalise from rodents to humans. One difference is that a greater proportion of brain development occurs before birth in primates than in rodents (Lupien et al., 2009). Furthermore, manipulation of the early environment in order to study the effects of early deprivation in humans is limited by ethical and practical constraints. In a landmark study aimed at investigating the effect of early deprivation, Nelson et al. (2007) conducted a randomised controlled trial to compare children fostered to local families, with children remaining in institutional care in Romanian orphanages. At four and a half years of age, those children randomised to foster care had substantially higher IQ scores (by over half a standard deviation) than children who remained in the impoverished environment provided by institutional care (Nelson et al., 2007). Although there was some indication that fostering before the age of 2 years was particularly important for IQ score, the study was not designed to test whether these first 2 years represent a truly sensitive period for cognitive development, as age of fostering was confounded by time spent in institutional care. Nevertheless, some support for the importance of the early environment, in the form of interaction between mothers and their infants, comes from a study of the

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timing of cleft lip repair on cognitive development (Murray et al., 2008).

Severe early childhood deprivation is relatively uncommon in the general population, and therefore the power to detect effects on cognition of those subgroups exposed to severe deprivation during specific periods will be limited, even in large studies. However, milder adversity is more common, such as that resulting from maternal illness, in particular maternal depression. Maternal depression has the potential to affect the care offered to infants in their 1st year of life, with studies demonstrating reduced maternal responsiveness with fewer contingent responses in depressed mothers (Field et al., 1988; Murray, Fiori-Cowley, Hooper, & Cooper, 1996).

Depression occurs commonly in women during the child bearing years (McManus, Meltzer, Brugha, Bebbington, & Jenkins, 2009). A number of longitudinal studies have shown that the children of mothers who had postnatal depression (PND) score poorly on cognitive measures early in development and that this effect is strongest in male offspring (Coghill, Caplan, Alexandra, Robson, & Kumar, 1986; Sharp et al., 1995). However, it is less clear whether these early developmental effects persist as the child grows older. One study, based in Cambridge, England, found that while direct effects were not evident when the children were aged 5 years (Murray, 1992; Murray, Hipwell, Hooper, Stein, & Cooper, 1996), follow up to 16 years found that PND affected boys' school performance through effects on early development and mother-child interaction (Murray et al., 2010). Another study, of a substantially more socioeconomically disadvantaged sample in South London (Hay et al., 2001; Sharp et al., 1995), found differences in IQ according to maternal PND were apparent both at age 11 and 16 (Hay, Pawlby, Waters, & Sharp, 2008). In general, associations between PND and lower child IQ have been more evident in high risk, rather than low risk samples (Murray, Halligan, & Cooper, 2010), suggesting that social disadvantage may moderate the relationship between postpartum depression and child cognitive development, with adverse effects being more common in children from socioeconomically disadvantaged backgrounds.

The postnatal period has long been considered a time of particular vulnerability to depression, but depressive symptoms are also common during pregnancy (Evans, Heron, Francomb, Oke, & Golding, 2001). Combining prevalence estimates in a meta-analysis, Gavin et al. (2005) found the period prevalence of depression during pregnancy to be 12.5%, with the point prevalence to be 4.9% during the second trimester, and 5.7% two months postnatally.

Patterns of depression during pregnancy and the first few postnatal years vary considerably between women, from single episodes, through recurrent episodes to chronic depression. More than half of those women who have high scores on symptoms of depression postnatally will have had high scores during early or late pregnancy. After the first postnatal year, the risk of depression remains high and many women experience a pattern of chronic depression extending from pregnancy and throughout the child's early years (Heron, O'Connor, Evans, Golding, & Glover, 2004).

It is important to take this variable course of maternal depression into account when considering the consequences for child development, particularly when investigating the effect of timing of exposure effects. As women who experience an episode of PND are more likely to have experienced depression during pregnancy, and are at increased risk of future episodes, PND acts as a marker of risk of depression at other times. Some studies that have included repeated measures of depression appear to indicate that chronicity, rather than timing of depression are important in child cognitive development (Brennan et al., 2000; Kurstjens & Wolke, 2001) although others have found independent effects of PND on behavioural outcomes (Hay, Pawlby, Waters, Perra, & Sharp, 2010). Samples have been too small to rigorously test timing effects, and few have measured antenatal depression prospectively furthermore simple adjustment for repeated measures is inadequate due to high levels of colinearity between adjacent measures.

Establishing when exposure to maternal depression is most harmful to cognitive development will guide when interventions should be offered and also contribute to understanding how these effects are manifested.

We set out to investigate whether the timing of maternal depression and the accumulation of exposure to depression over time was important in child cognitive development. In particular, we tested the hypothesis that the postnatal period is a sensitive period for the effect of maternal depression on child cognitive development. By sensitive period in this context we mean that the effect of maternal depression occurring at a specific point in time is different (we expect greater) from at other times (which are equivalent in their effect). We also tested whether the antenatal or preschool period was a sensitive period, and whether these effects would be strongest in children from socioeconomically disadvantaged backgrounds and strongest in boys. To overcome the limitations of previous studies, we used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) (http://www.bristol.ac.uk/alspac). This longitudinal study collected data prospectively starting in pregnancy, included repeated measures of maternal mood and a range of relevant confounding variables. It is sufficiently large to allow investigation of subgroups of women according to the course of their depressive symptoms overtime thus allowing a life-course model-building approach to be used.

Methods

The ALSPAC enrolled women who were resident in Avon, England and in the early stages of pregnancy between 1 April 1991 and 31 December 1992. Postal questionnaires were sent at regular intervals during pregnancy and following child birth, these included measures of maternal depressive symptoms. Mothers and their children were invited to attend clinics annually from aged 7 and this report concerns those children who attended the clinic at aged 8 years when data collection included a measure of IQ. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

Our starting sample consists of 6,735 children who were from singleton births, attended the 8-year research clinic, completed an IQ measure and scored 70 or above.

Measures

Depression. The Edinburgh Postnatal Depression Scale (EPDS) was used to measure symptoms of depression (Cox, Holden, & Sagovsky, 1987). The EPDS focuses on the cognitive and affective features of depression rather than somatic symptoms. Although this scale was developed to screen for depression in women following childbirth, it has also been validated for use during pregnancy with a sensitivity of between 100% and 73% and specificity of between 87% and 82% for identifying major depression (Adouard, Glangeaud-Freudenthal, & Golse, 2005; Murray & Cox, 1990). There have been numerous postnatal validation studies and for the > 12 cut off, sensitivity varies between 100% and 68% and specificity between 96% and 93% (Shakespeare, 2001) and is comparable to other screening instruments (Lee, Yip, Chiu, Leung, & Chung, 2001). For the ALSPAC sample, we found a sensitivity of 86% and specificity of 78% when compared to a semi-structured diagnostic interview (Thorpe, 1993). The EPDS was included in the postal questionnaires and this study concerns data collected at 18 and 32 weeks of pregnancy, 8 weeks and 8 months in the first postnatal year and then 21 and 33 months in the preschool period. We defined antenatal depression as high EPDS score (> 12) at 18 or 32 weeks of pregnancy, PND as a high EPDS score (> 12) at either 8 weeks or 8 months postnatally, and preschool depression as a high EPDS score (> 12) at either 21 weeks or 33 months postnatally.

Child cognitive ability. The IQ was assessed with the Wechsler (1991) intelligence scale for children (WISC–III) which was the most recent version at the time. This was administered during a research assessment clinic by trained researchers. To shorten the time taken on the IQ test during the clinic, alternate items of each subtest were used (always starting with item number 1 in the standard form), except for the coding test which was used in its complete form. These analyses concern the full-scale IQ scores derived by multiplying the raw scores to generate scores comparable to the full test version. Short forms of the WISC that reduce the number of items have been shown to produce good estimates of full-scale IQ (Silverstein, 1968).

Statistical analyses

We based our approach to analysis on a life-course model building framework proposed by Mishra et al. (2009) for repeated measures. We compared models nested within a saturated model in which both the order and binary value of the exposure (depression yes/no) contributed to the outcome. The best fitting model, nested within this saturated model, was then adjusted for potential confounders. We used this approach with child IQ as the outcome variable and occurrence of maternal depression (yes/no) as the main exposure of interest. We restricted our analyses to those children scoring 70 or above on the full scale IQ to avoid including infants who may have substantial neurological problems which could provoke depression in mothers (n = 6,735). We then fitted models according to our hypotheses of interest on all cases that also had complete measures of depression (n = 5,029). We compared three hierarchical models each with different assumptions concerning the effect of maternal depression on child cognitive ability. These were (a) the saturated model in which the assumption is that the effect would vary according to any possible pattern of depression, (b) the sensitive period models in which the assumption is that the effect would be different (e.g. stronger) at any specified period but the same at the other times, and (c) an accumulation model in which the assumption is that the effect of depression would be the same at each time point.

The saturated model comprised all eight possible patterns of depression occurring across three periods. This was equivalent to fitting an ordinary least squares linear regression model with full factorial design on the binary depression variables (Mishra et al., 2009). The sensitive period models comprised three specifications of the model of interest according to the period investigated namely, antenatal, postnatal or preschool. These were nested within the saturated model. A sensitive period model assumed a different main effect for the period of interest (we expected greater) from the main effects at other time points which were the same as each other. No interactions between time points were included in the models. The accumulation model assumed the same effect for each time period by setting equality constraints for all the main effects of depression and also excluded any interaction terms. This model is nested within each sensitive period model. Models nested within one another were compared using the likelihood ratio test. As the sensitive period models were not nested within each other, they were compared using the Bayesian Information Criterion (BIC).

Model comparisons were made without imputation as likelihood ratio tests and BIC cannot be computed using imputed data sets (Graham, 2009). The model comparisons were also made without adjustment as some potential confounders would operate differently according to the timing model comparisons and this would make the results more difficult to interpret. This would also reduce the sample size. We ran multiple imputations of our covariates by chained equations (Rubin, 1997; Sterne et al., 2009; Van Buuren, Boshuizen,

& Knook, 1999) for the best fitting models, to overcome the problem of missing data and reduced sample sizes. We ran 10 imputations of 10 cycles each with the command *ice* in stata (Royston, 2005). The imputation model included all six repeated measures of depression within the periods of interest (subsequently transformed and recoded as three complete binary variables), and the child's IQ. All covariates in the fully adjusted models were included in the imputation model along with variables related to the socioemotional environment of the household (e.g. aggression/affection scores; crowding; parental substance use, child educational attainment). A total of 43 variables entered the imputation process. Results across multiply imputed datasets were combined according to Rubin's (1997) rules. This multiple imputation technique is based on the assumption that data are missing at random, given the observed characteristics of the individuals. We imputed missing data to include all those in our starting sample of 6,735, that is, those mothers whose children attended the clinic assessment and completed a WISC scoring ≥ 70. We avoided imputing the outcome variable, IQ, as this was likely to increase the noise of the estimates in the absence of a strong predictor of IQ (Graham, 2009). We reported estimated results for the sensitive period models and for the accumulation model before adjustment (excluding and including imputed data) and after adjustment (including imputed data only). Sensitivity analyses were conducted using different thresholds on the EPDS scale. Adjustment was made for parity (0, 1, 2 or more), maternal age at delivery, smoking and drinking during pregnancy, parental social class, maternal education, disposable income and child's gender. We examined interactions of maternal depression with gender and separately, measures of social class. Additionally, we made a separate adjustment for birth weight and any breast feeding after birth (yes/no) which have been shown to relate to cognitive development.

Results

Of the 13,615 eligible children, 6,735 (49.5%) attended the 8-year assessment clinic and had complete WISC scores with a full-scale IQ score of ≥ 70. Their mean (*SD*) full-scale IQ was 101.4 (16.6). A total of 5,029 mothers of these 6,735 children had depression scores available for all three periods antenatal, postnatal and preschool the mean (*SD*) full-scale IQ score for their children was 105.3 (16.3). Of these, 4,406 women also had complete data on all potential confounders.

Differences between those with complete data (on maternal depression and child IQ) and those with missing data show that those with missing data were more likely to have antenatal depression (27.6% cf. 18.6%, $p > .001$), PND (18.8% cf. 13.1%, $p > .001$), a male child (52.9% cf. 49.3%, $p > .001$), not breast feed (30.2% cf. 16.5%, $p > .001$), to already have at least one child (55.5% cf. 53.5%, $p > .001$), smoked during pregnancy (32.3% cf. 18.2%, $p > .001$), drunk > 1 glass of alcohol per week during pregnancy (44.8% cf. 29.2%, $p > .001$), come from social class III to V (51.2% cf. 36.8%, $p > .001$), reached a lower maximum educational level (< 1 O-level, 31.5% cf. 17.0%, $p > .001$), have a lower household income (lowest quintile, 26.3% cf. 13.3%, $p > .001$), be younger at delivery (mean age 27.1 cf. 29.4, $p > .001$) a lower birth weight child (mean 3.39 kg cf. 3.46 kg, $p > .001$).

Of the 5,029 women with depression data for all three periods, 936 (18.6%) had high scores suggesting antenatal depression, 660 (13.1%) had high scores suggesting PND, and 819 (16.3%) high scores suggesting depression in the preschool period. Those with depression on all three occasions ($n = 270$, 5.4%) had children with IQ scores of 101.97 (95% CI: 100.1–103.8) and those with depression on none of the three occasions ($n = 3,519$, 70.0%) had children with IQ scores of 106.7 (95% CI: 106.2–107.3). Child IQ scores for all maternal depression patterns are shown in Table 1.

The characteristics of those with PND compared to those without are shown in Table 2. Compared to nondepressed mothers, those with PND were more likely to have had antenatal depression, drink alcohol during pregnancy, smoke during pregnancy, have lower birth weight infant, come from social class IV or V, have lower household income, have less formal education, be younger, and already have children. They were also less likely to breast feed. The children of mothers who did experience PND had an IQ score that was 2.4 points lower (95% confidence interval between 3.6 and 1.1 points lower) than those whose mothers did not.

Model comparisons

All three sensitive period models and the simple accumulation model are nested within the saturated model. The results of the four comparisons: (a) the

Table 1 The pattern of high maternal depression scores over time and child IQ aged 8 years ($N = 5,059$)

Antenatal	Postnatal	Preschool	*n*	%	IQ	*SE*	95% CI
No	No	No	3,519	69.97	106.74	0.26	106.22–107.26
Yes	No	No	400	7.95	103.10	0.78	101.57–104.64
No	Yes	No	180	3.58	106.55	1.17	104.26–108.84
No	No	Yes	295	5.87	105.72	0.91	103.93–107.50
Yes	Yes	No	111	2.21	104.09	1.49	101.18–107.00
Yes	No	Yes	155	3.08	101.43	1.26	98.96–103.89
No	Yes	Yes	99	1.97	103.39	1.57	100.31–106.48
Yes	Yes	Yes	270	5.37	101.97	0.95	100.10–103.83

Table 2 Characteristics of those women with Edinburgh Postnatal Depression Scale score > 12 at 2 months and or 8 months postnatally (*N* varies as a result of missing data for some variables)

	Postnatal depression		No postnatal depression		
	N or mean	% or *SD*	*N* or mean	% or *SD*	*p*-Value
Total	1,707	16.1	8,879	83.9	
Antenatal variables					
Antenatal depression	953	62.5	1,118	14.1	< .001
Breast-feeding	1,090	73.5	6,616	77.8	< .001
Alcohol use during pregnancy					
< 1 glass/week	1,075	63.8	6,277	70.7	< .001
Other	524	31.1	2,332	26.3	
1+ glasses/day	87	5.2	264	3.0	
Smoking during pregnancy					
Never	1,050	62.9	6,871	78.0	< .001
1–19 max./day	444	26.6	1,574	17.9	
20+ max./day	175	10.5	362	4.1	
Birthweight, g mean (*SD*)	3,392	538	3,454	507	< .001
Social and demographic variables					
Social class					
IV or V	105	7.3	395	4.8	< .001
III	580	40.4	3,044	37.2	
II	582	40.5	3,552	43.4	
I	169	11.8	1,199	14.6	
Household income					
(Lowest) I	349	27.3	1,271	16.9	< .001
II	283	22.2	1,444	19.3	
III	222	17.4	1,555	20.7	
IV	227	17.8	1,564	20.9	
(Highest) V	196	15.4	1,668	22.2	
Highest maternal education					
<O-level	442	30.1	1,805	21.9	< .001
O-level	496	33.8	3,132	37.9	
A-level	337	23.0	2,086	25.3	
Degree	192	13.1	1,238	15.0	
Child gender (female)	821	48.1	4,315	48.6	.704
Maternal age at delivery mean (*SD*)	28.0	5.3	28.6	4.7	< .001
Parity					
0	603	38.5	3,951	46.4	< .001
1	605	38.7	2,966	34.8	
2 or more	357	22.8	1,595	18.7	

postnatal sensitive with the saturated model, (b) the antenatal sensitive with the saturated model, (c) the preschool sensitive with the saturated model, and (d) the simple accumulation with the saturated model are shown in Table 3. None of these models could be excluded as an explanation for the relationship between maternal depression and child IQ, as all models fitted the data as well as the saturated model. This was evident by both the likelihood ratio test (all $p > .06$) and the BIC values (all delta BIC > 32). It was not possible to compare the sensitive period models directly as they are not nested within one another. Indirect comparisons were, however, possible as the simple accumulation model is nested in each sensitive period model. Three further comparisons were made (a) the accumulation with the postnatal sensitive model, (b) the accumulation with the antenatal sensitive model, and (c) the accumulation with the preschool sensitive model. The accumulation model was not as good as either the antenatal sensitive (likelihood ratio test, $p < .01$) or the postnatal sensitive (likelihood ratio test, $p = .017$), at explaining the data. When we ran the same model comparisons moving the threshold for depression higher to > 15 and lower to < 9, only the sensitive antenatal model and not the postnatal sensitive model was consistently a better fit than the accumulation model itself (data available on request).

Indirect comparison of sensitive period models made by comparing BIC showed that the antenatal, rather than the postnatal or the preschool sensitive period model, fitted the data slightly better with regard to the effect of maternal depression on child IQ (lowest BIC of these three models in Table 3). We therefore ran regression models for the antenatal sensitive period and investigated the effect of adjusting for potential confounders on the relationship of antenatal depression with child IQ. As previously stated, the sensitive period models allowed the period in question to vary but the other two periods to be fixed as equivalent in their effect on the outcome. There was an unadjusted effect of ante-

Table 3 Comparison of life-course models under different assumptions according to the effect of maternal depression at different times on child IQ. Complete case analysis (N = 5,029), unadjusted

Life-course modelling comparisons				
Test model (a)	Nest model (b)	Δdf ($b - a$)	p-Value	ΔBIC ($b - a$)
Comparison to saturated model				
Sensitive postnatal[a]	Saturated	5	.40	37.5
Sensitive antenatal[a]	Saturated	5	.62	39.1
Sensitive preschool[a]	Saturated	5	.063	32.1
Accumulation[a]	Saturated	6	.094	40.3
Comparison to postnatal sensitive period model				
Accumulation	Sensitive postnatal	1	.017[b]	2.8
Comparison to antenatal sensitive period model				
Accumulation	Sensitive antenatal	1	< .01[b]	1.2
Comparison to preschool sensitive period model				
Accumulation	Sensitive preschool	1	.56	8.2

Test model, model being tested against the comprehensive nest model.
[a]Bayesian Information Criteria (BIC) values for antenatal sensitive 41,958.82, postnatal sensitive 41,960.44 and preschool sensitive 41,965.78, accumulation 41,957.6. [b]These likelihood ratio tests indicate that the test model does not fit the data as well as the nest model.

natal depression on IQ, −3.34 (95% CI: −4.59 to −2.09, $p < .001$) independent of depression occurring at other times; this was attenuated following adjustment for potential confounding factors, −0.64 (95% CI: −1.68 to 0.40; Table 4). By way of sensitivity analysis we repeated these analyses with a lower (< 9) cut off for EPDS depression and higher (> 15) cut off. Following complete adjustment and imputation of missing values, the effect of antenatal depression remained; −0.92 (95% CI: −1.74 to −0.1) for the lower cut off, and −2.0 (95% CI: −3.5 to −0.4) for the higher cut off.

We repeated the same regression analyses for postnatal sensitive, preschool sensitive and accumulation models. For the postnatal sensitive model, with the standard cut off, there was no unadjusted effect (−0.19, 95% CI: −1.5 to 1.1) or effect following adjustment (−0.25, 95% CI: −1.42 to 0.92). For the preschool sensitive model, with the standard cut off there was a small unadjusted association (−1.08, 95% CI: −2.29 to 0.13) changing little following adjustment (−1.01, 95% CI: −2.11 to 0.08). The accumulation model indicated an association (−1.63, 95% CI: −2.1 to −1.17) for each occasion when depression occurred which attenuated following adjustment (−0.65, 95% CI: −1.08 to −0.23).

There was no interaction between postnatal, antenatal or preschool occurrence of depression and either child's gender, maternal education, social class or household disposable income on child IQ. Any moderation by these demographic or socioeconomic factors on the relationship between maternal depression and child's IQ was therefore not evident.

Discussion

In this study, maternal PND occurring in the 1st year after birth did not have an independent influence on child cognitive function at age 8. The postnatal period did not appear to be a sensitive one for exposure to maternal depression.

These findings indicate that there are no long-lasting effects of PND of the severity seen in community samples such as this, on child cognitive development as measured by IQ that are any worse than when depression occurs at other times. This contrasts with the findings of Hay et al. (2001) who found effects of PND that persist to age 16. This study was conducted in a socioeconomically disadvantaged population in south London and the effect was strongest in boys. Although depression was common in this population, the small sample size

Table 4 Relationship between antenatal depression and child IQ aged 8

Model assumption	Depression timing	N	Coefficient	95% CI	p-Value
Sensitive antenatal model					
Unadjusted	Antenatal	5,029	−3.34	−4.59 to −2.09	<.001
	Depression during other periods		−0.89	−1.71 to 0.08	.032
Unadjusted multiple imputation	Antenatal	6,735	−3.19	−4.33 to −2.06	<.001
	Depression during other periods		−0.75	−1.50 to 0.00	.049
Adjusted with multiple imputation[a]	Antenatal	6,735	−0.69	−1.73 to 0.35	.19
	Depression during other periods		−0.68	−1.36 to 0.00	.051
Adjusted with multiple imputation[b]	Antenatal	6,735	−0.64	−1.68 to 0.40	.23
	Depression during other periods		−0.66	−1.34 to 0.01	.052

[a]Adjusted for maternal parity (0, 1, 2 or more), maternal age, smoking (maximum no. cigarettes/day), drinking (maximum no. drinks/week) during pregnancy, parental social class, maternal education, disposable income and child's gender. [b]Adjusted for all in (a) and also birth weight and breast feeding.

may have been inadequate to detect other sensitive periods and the method of data analysis was limited by high levels of colinearity between adjacent measures of depression. We did not find evidence of any differential effect by child's gender and maternal socioeconomic circumstances on the association between maternal depression and child IQ to account for these different findings.

Our results are consistent with other studies that found no postnatal sensitive period. These studies reported a contribution from accumulated exposure over time for child cognitive and other outcomes (Hammen & Brennan, 2003; Kurstjens & Wolke, 2001), although accumulation was not the best model for our data, we did identify that the effect of maternal depression was not restricted to a single time period. One potential explanation for the effect of continuing depression is that mothers who experience this carry other risks not measured here which cause their offspring to have poorer cognitive development. This may include shared genetic vulnerability or maternal antisocial lifestyle which can impact on child cognitive development (Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005). However, unlike the data we have analysed here from ALSPAC, studies that found chronicity rather than timing of maternal depression was important in cognitive development, did not measure mood during pregnancy and therefore could not estimate the contribution of antenatal depression.

Our analyses suggest that the antenatal occurrence of depression might be more important than depression at other times, although the effects were small following adjustment (and for the standard cut off included no effect within the confidence interval). The effect was stronger for those with more severe symptoms of depression. Accumulation of depression over time was also associated with lower child IQ following adjustment. We have established that there is an effect of antenatal depression but found only weak evidence that the antenatal period is a sensitive one.

Our findings support other observations suggesting that what happens during pregnancy plays a role in health and development in postnatal life (Barker, 1998). This is consistent with previous findings from this sample and others indicating that the antenatal period may be more important than the postnatal period in a range of aspects of child development (Deave, Heron, Evans, & Emond, 2008; Hay et al., 2010; O'Connor, Heron, Golding, & Glover, 2003).

There is a growing body of work investigating the fetal origins of adult disease and the findings reported in this article are consistent with a small specific effect of depression during pregnancy on cognitive development. We were able to control for potentially important explanations such as smoking during pregnancy and drinking alcohol, as well as low birth weight, which are all more common amongst those who are depressed during pregnancy.

The way antenatal depression effects child cognitive development is likely to be different from depression occurring at other times. One possible mechanism is that raised maternal cortisol, which occurs during depression (Arborelius, Owens, Plotsky, & Nemeroff, 1999) causes a rise in fetal cortisol and impairs neurodevelopment. Animal studies have found impaired hippocampal function in the offspring of rats administered cortisol during pregnancy and those exposed to acute stress at this time (Lemaire, Koehl, Le Moal, & Abrous, 2000). There are long-term effects on hypothalamic–pituitary–adrenal axis function of prenatal stress which could have effects on postnatal neurodevelopment (Lupien et al., 2009).

An alternative explanation for the importance of antenatal depression for cognitive development is the disruption of the programming of maternal responsiveness that occurs in pregnancy in preparation for the parenting role. There is evidence that responsiveness to infant faces changes during pregnancy and that this is disrupted by depression occurring at this time (Pearson, Cooper, Penton-Voak, Lightman, & Evans, 2010). If this preparation is impaired, then mothers who were depressed during pregnancy, even if recovered postnatally, may show poorer postnatal contingent responses. This may impair the development of important neurocognitive functions. As there were no detailed measures of mother-child interactions in the postpartum period in this sample, it was not possible to test this hypothesis; nevertheless, it is consistent with other reports that these interactions in the first few months are particularly important for cognitive development (Lemaire et al., 2000).

The Avon Longitudinal Study of Parents and Children has a number of strengths, including the large sample size, the range of potential confounding variables and the frequency of repeated depressive symptom measures, with assessment starting during pregnancy. However, one limitation of observational studies such as this is that unmeasured confounding factors might explain the apparent effects of depression on IQ in particular situations. Without random allocation to period of exposure, definite conclusions concerning a sensitive period cannot be drawn. There were, in addition, no diagnostic interviews for depression, and it is possible that depressive symptoms may be different during pregnancy (Kammerer et al., 2009); however, the EPDS has good validity during pregnancy (Thorpe, 1993) as well as postnatally, and our previous analyses of these data do not indicate any difference in symptom profile at different times (Evans et al., 2001). We have not investigated whether the effects we report here are due to anxiety symptoms rather than depression. One reason is that there is such a strong relationship between generalised anxiety and depression that it is difficult to separate them; indeed, some have argued they should be combined in diagnostic systems. Such colinearity makes it inappropriate to include anxiety in models

used here. As with many longitudinal studies, there are considerable missing data on one or more of the variables of interest. It is clear that the assumption that these data are missing completely at random is not correct. Mothers with higher depressive symptoms were less likely to have complete data and their children less likely to attend clinic. This bias could lead to an underestimate of the effect size. When we increased the sample size by imputing data for missing values using a predictive model based on chained equations, we found broadly similar results indicating that biases were not sufficient to lead to erroneous conclusions.

It is notable that the effects of maternal age, birth weight, social class, household income, maternal education and parity on child IQ are all quite large and independent of depressive symptoms. Nevertheless, interventions aimed at identifying and reducing depression during pregnancy are likely to have benefits, not only through effects on the direct association but also through other pathways such as reducing smoking during pregnancy, and reducing postnatal and later depression. There is growing evidence concerning the effects of paternal mood on child outcomes including from the ALSPAC data set (Ramchandani et al., 2008) and a more comprehensive model would investigate how fathers and others influence the relationships investigated here.

We conclude that the postnatal period is not a sensitive one with regard to the effects of maternal depression on cognitive development. Maternal depression has an effect whenever it occurs, with a slightly stronger effect of antenatal depression. Intervention during pregnancy may thus provide a valuable opportunity to improve child development.

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Key points

- It is known that maternal depression is associated with poorer child developmental outcomes.
- The postnatal period is not a sensitive one for the effect of exposure to maternal depression on child cognitive development.
- Maternal depression across all occasions is important in child cognitive development and may have a slightly stronger effect when it occurs antenatally.
- These effects do not differ according to child gender or maternal social class.
- Treating depression during pregnancy may confer benefit on child development.

References

Adouard, F., Glangeaud-Freudenthal, N.M.C., & Golse, B. (2005). Validation of the Edinburgh postnatal depression scale (EPDS) in a sample of women with high-risk pregnancies in France. *Archives of Women's Mental Health*, *8*, 89–95.

Arborelius, L., Owens, M.J., Plotsky, P.M., & Nemeroff, C.B. (1999). The role of corticotropin-releasing factor in depression and anxiety disorders. *Journal of Endocrinology*, *160*, 1–12.

Barker, D.J.P. (1998). In utero programming of chronic disease. *Clinical Science*, *95*, 115–128.

Brennan, P.A., Hammen, C., Andersen, M.J., Bor, W., Najman, J.M., & Williams, G.M. (2000). Chronicity, severity, and timing of maternal depressive symptoms: Relationships with child outcomes at age 5. *Developmental Psychology*, *36*, 759–766.

Coghill, S.R., Caplan, H.L., Alexandra, H., Robson, K.M., & Kumar, R. (1986). Impact of postnatal depression on cognitive development in young children. *British Medical Journal*, *292*, 1165–1167.

Cox, J.L., Holden, J.M., & Sagovsky, R. (1987). Detection of postnatal depression—Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry*, *150*, 782–786.

de Kloet, E.R., & Oitzl, M.S. (2003). Who cares for a stressed brain? The mother, the kid or both? *Neurobiology of Aging*, *24*(Suppl. 1), S61–S65.

Deave, T., Heron, J., Evans, J., & Emond, A. (2008). The impact of maternal depression in pregnancy on early child development. *British Journal of Obstetrics and Gynaecology*, *115*, 1043–1051.

Enthoven, L., de Kloet, E.R., & Oitzl, M.S. (2008). Effects of maternal deprivation of CD1 mice on performance in the water maze and swim stress. *Behavioural Brain Research*, *187*, 195–199.

Evans, J., Heron, J., Francomb, H., Oke, S., & Golding, J. (2001). Cohort study of depressed mood during pregnancy and after childbirth. *British Medical Journal*, *323*, 257–260.

Field, T., Healy, B., Goldstein, S., Perry, S., Bendell, D., Schamberg, S., Zimmerman, E., & Kuhn, G. (1988). Infants

of depressed mothers show "depressed" behavior even with non-depressed adults. *Child Development*, *60*, 1569–1579.
Gavin, N.I., Gaynes, B.N., Lohr, K.N., Meltzer-Brody, S., Gartlehner, G., & Swinson, T. (2005). Perinatal depression: A systematic review of prevalence and incidence. *Obstetrics and Gynecology*, *106*, 1071–1083.
Graham, J.W. (2009). Missing data analysis: Making it work in the real world. *Annual Review of Psychology*, *60*, 549–576.
Hammen, C., & Brennan, P.A. (2003). Severity, chronicity, and timing of maternal depression and risk for adolescent offspring diagnoses in a community sample. *Archives of General Psychiatry*, *60*, 253–258.
Hay, D.F., Pawlby, S., Sharp, D., Asten, P., Mills, A., & Kumar, R. (2001). Intellectual problems shown by 11-year-old children whose mothers had postnatal depression. *Journal of Child Psychology and Psychiatry*, *42*, 871–889.
Hay, D.F., Pawlby, S., Waters, C.S., Perra, O., & Sharp, D. (2010). Mothers' antenatal depression and their children's antisocial outcomes. *Child Development*, *81*, 149–165.
Hay, D.F., Pawlby, S., Waters, C.S., & Sharp, D. (2008). Antepartum and postpartum exposure to maternal depression: Different effects on different adolescent outcomes. *Journal of Child Psychology and Psychiatry*, *49*, 1079–1088.
Heron, J., O'Connor, T.G., Evans, J., Golding, J., & Glover, V. (2004). The course of anxiety and depression through pregnancy and the postpartum in a community sample. *Journal of Affective Disorders*, *80*, 65–73.
Kammerer, M., Marks, M.N., Pinard, C., Taylor, A., von Castelberg, B., Künzli, H., & Glover, V. (2009). Symptoms associated with the DSM IV diagnosis of depression in pregnancy and post partum. *Archives of Women's Mental Health*, *12*, 135–141.
Kim-Cohen, J., Moffitt, T.E., Taylor, A., Pawlby, S.J., & Caspi, A. (2005). Maternal depression and children's antisocial behavior: Nature and nurture effects. *Archives of General Psychiatry*, *62*, 173–181.
Kurstjens, S., & Wolke, D. (2001). Effects of maternal depression on cognitive development of children over the first 7 years of life. *Journal of Child Psychology and Psychiatry*, *42*, 623–636.
Lee, D.T.S., Yip, A.S.K., Chiu, H.F.K., Leung, T.Y.S., & Chung, T.K.H. (2001). Screening for postnatal depression: Are specific instruments mandatory? *Journal of Affective Disorders*, *63*, 233–238.
Lemaire, V., Koehl, M., Le Moal, M., & Abrous, D.N. (2000). Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 11032–11037.
Liu, D., Diorio, J., Day, J.C., Francis, D.D., & Meaney, M.J. (2000). Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neuroscience*, *3*, 799–806.
Lupien, S.J., McEwen, B.S., Gunnar, M.R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews. Neuroscience*, *10*, 434–445.
McManus, S., Meltzer, H., Brugha, T., Bebbington, P., & Jenkins, R. (2009). *Adult psychiatric morbidity in England, 2007: Results of a household survey*. London, UK: NHS Information Centre for Health and Social Care.
Mishra, G., Nitsch, D., Black, S., De, S.B., Kuh, D., & Hardy, R. (2009). A structured approach to modelling the effects of binary exposure variables over the life course. *International of Journal of Epidemiology*, *38*, 528–537.
Murray, L. (1992). The impact of postnatal depression on infant development. *Journal of Child Psychology and Psychiatry*, *33*, 543–561.
Murray, L., Arteche, A., Fearon, P., Halligan, S., Croudace, T., & Cooper, P. (2010). The effects of maternal postnatal depression and child sex on academic performance at age 16 years: A developmental approach. *Journal of Child Psychology and Psychiatry*, *51*, 1150–1159.
Murray, D., & Cox, J.L. (1990). Screening for depression during pregnancy with the Edinburgh Depression Scale (EPDS). *Journal of Reproductive and Infant Psychology*, *8*, 99–107.
Murray, L., Fiori-Cowley, A., Hooper, R., & Cooper, P. (1996). The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Development*, *67*, 2512–2526.
Murray, L., Halligan, S., & Cooper, P.J. (2010). Effects of postnatal depression on mother-infant interactions, and child development. In T. Wachs, & G. Bremmer (Eds.), *Wiley-Blackwell handbook of infant development* (pp. 192–220). Oxford, UK: Wiley-Blackwell.
Murray, L., Hentges, F., Hill, J., Karpf, J., Mistry, B., Kreutz, M., … & Cleft Lip and Palate Study Team. (2008). The effect of cleft lip and palate, and the timing of lip repair on mother-infant interactions and infant development. *Journal of Child Psychology and Psychiatry*, *49*, 115–123.
Murray, L., Hipwell, A., Hooper, R., Stein, A., & Cooper, P. (1996). The cognitive development of 5-year-old children of postnatally depressed mothers. *Journal of Child Psychology and Psychiatry*, *37*, 927–935.
Nelson, C.A., III, Zeanah, C.H., Fox, N.A., Marshall, P.J., Smyke, A.T., & Guthrie, D. (2007). Cognitive recovery in socially deprived young children: The Bucharest Early Intervention Project. *Science*, *318*, 1937–1940.
Novak, M.A., & Harlow, H.F. (1975). Social recovery of monkeys isolated for 1st year of life. 1. Rehabilitation and therapy. *Developmental Psychology*, *11*, 453–465.
O'Connor, T.G., Heron, J., Golding, J., & Glover, V. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry*, *44*, 1025–1036.
Pearson, R.M., Cooper, R.M., Penton-Voak, I.S., Lightman, S.L., & Evans, J. (2010). Depressive symptoms in early pregnancy disrupt attentional processing of infant emotion. *Psychological Medicine*, *40*, 621–631.
Ramchandani, P.G., Stein, A., O'Connor, T.G., Heron, J., Murray, L., & Evans, J. (2008). Depression in men in the postnatal period and later child psychopathology: A population cohort study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 390–398.
Royston, P. (2005). Multiple imputation of missing values: Update. *Stata Journal*, *5*, 188–201.
Rubin, D. (1997). *Multiple imputation of nonresponse in surveys*. New York: Wiley.
Shakespeare, J. (2001). *Evaluation of screening for postnatal depression against the NSC handbook criteria*. London: National Screening Committee.
Sharp, D., Hay, D.F., Pawlby, S., Schmucker, G., Allen, H., & Kumar, R. (1995). The impact of postnatal depression on boys' intellectual development. *Journal of Child Psychology and Psychiatry*, *36*, 1315–1336.
Silverstein, A.B. (1968). Validity of a new approach to the design of WAIS WISC and WPPSI short forms. *Journal of Consulting and Clinical Psychology*, *32*, 478–479.
Sterne, J.A.C., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., … & Carpenter, J.R. (2009). Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *British Medical Journal*, *338*, b2393; doi: 10.1136/bmj.b2393.
Thorpe, K. (1993). A study of Edinburgh Postnatal Depression Scale for use with parent groups outside the postpartum period. *Journal of Reproductive and Infant Psychology*, *11*, 119–125.
Van Buuren, S., Boshuizen, H.C., & Knook, D.L. (1999). Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in Medicine*, *18*, 681–694.
Wechsler, D. (1991). *Manual for Wechsler intelligence scale for children–Revised*. San Antonio, TX: Psychological Corporation.

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