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STRESSFUL LIFE EVENTS DURING PREGNANCY AND OFFSPRING DEPRESSION: EVIDENCE FROM A PROSPECTIVE COHORT STUDY

Running Title: Prenatal Stress and Offspring Depression

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ABSTRACT

Objective: The fetal programming hypothesis posits that in-utero exposure to stress can alter prenatal brain development and lifelong stress response. However, human studies linking objective prenatal stressors to offspring mental illness, especially depression, are rare. The purpose of this study was to examine the association between mothers' exposure to prenatal stressful life events (SLEs) and offspring depression.

Methods*:* The sample comprised 10,569 members of a prospective population-based cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC). Mothers reported on the occurrence and impact of 42 prenatal SLEs. Offspring depressive symptoms were assessed using a computerized version of the *Clinical Interview Schedule-Revised* (CIS-R) at age 17/18, as well as 13 self-report statements from the *Short Mood and Feelings Questionnaire* (SMFQ) at six time points from ages 10/11 to 18/19. Latent Class Growth Analysis (LCGA) was used to identify trajectories of depressive symptoms across adolescence.

Results: After adjusting for potential confounders, a one-unit increase in maternal SLE scores (range:0-168) during gestation was associated with increased offspring depressive symptoms (β=0.07, p<.01) and major depression (OR:1.03 95%CI:1.01,1.06) at age 17/18. LCGA revealed four trajectories of depressive symptoms. High maternal SLEs (4^{th} quartile) were associated with membership in the trajectory characterized by stable, high levels of depression from age 10/11 to 18/19 (OR:1.72, 95%CI:1.09,2.71).

Conclusion: These results provide support for the fetal programming hypothesis, demonstrating that prenatal exposure to acute stress is associated with offspring depression in adolescence. Stress management may be of benefit for expectant mothers.

INTRODUCTION

The fetal programming hypothesis posits that in-utero exposure to stress can alter prenatal development, with lasting effects on offspring health and behavior. [1] Specifically, maternal stress during sensitive periods of fetal development is thought to affect development of the hypothalamic-pituitary-adrenal (HPA) axis, permanently altering the stress response. [2] Prenatal stress has been linked to increased HPA reactivity and depressive-like behavior in rats and rhesus monkeys. [3–5] Investigations of fetal programming with humans have often used low birth weight as a proxy for prenatal stress, with several studies demonstrating a link between low birth weight and later depressive symptoms. [6,7] Other studies have linked mothers' perceived stress and anxiety during pregnancy to behavioral and emotional problems in childhood.[8–12] However, such measures of anxiety may capture chronic, trait-like anxiety that extend beyond the prenatal period, rendering it unclear whether chronic stress or stress onset during pregnancy is most important to predicting offspring mental health outcomes. One study reported that mothers' antenatal depression predicted offspring major depression at 18 years, independent of mothers' postnatal depression suggesting the onset during pregnancy is most important.[13]

A limited number of studies have examined the impact of objective stressors during pregnancy on offspring mental health. Studies of mothers who were pregnant during natural disasters, wars, and periods of famine have revealed increased risk of psychosis, as well as behavioral and emotional maladjustment in their offspring.[14–16] Prenatal paternal death has also been associated with increased risk of psychiatric disorder.[17] One Danish population-based study reported that death of a relative during the first trimester of pregnancy was associated with higher risk of schizophrenia in offspring.[18] Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, Dorrington and colleagues showed that prenatal exposure to

stressful life events was associated with psychotic symptoms – however, this association was no longer significant once models were adjusted for prenatal anxiety and depression.[19] Limited evidence suggests this association does not extend to other offspring mental health disorders, but the association between prenatal stress and offspring depression has rarely been studied in humans. In one notable exception, Brown and colleagues reported increased risk of hospitalization for major affective disorder among offspring of mothers pregnant during the Dutch famine of 1944.[20] The use of objective stressors appropriately disentangles the effect of stressful events from coping strategies of the mother, but further research must use a broader range of events so as to appropriately ascertain the burden of stress in pregnancy.

The primary aim of the project was to examine the long-term association between mothers' exposure to stressful life events during pregnancy and offspring depression in adolescence in a prospective cohort study. Our primary hypothesis was that in-utero exposure to major stressful events would be associated with increased risk of depression and depressive symptomatology in adolescence, and that these associations would persist after adjusting for the effects of chronic stressors such as low socioeconomic status, maternal depression, and stressful events in the postnatal period.

METHOD

Sample

The sample was drawn from the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing population-based study of the determinants of child health and development. The initial cohort consisted of 14,062 pregnant women with estimated delivery dates between April 1, 1991 and December 31, 1992. All participants provided informed consent, the study was approved by the ALSPAC Ethics and Law committee, and these analyses were approved by the [redacted] Research Ethics Board. Detailed information about sample characteristics and response rates is available online (http://www.bris.ac.uk/alspac). For information on all available ALSPAC data see the fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary).

Inclusion and exclusion criteria for the sample of complete cases are presented in the Supplemental Figure.

Measures

Exposures

Stressful life events (SLEs) in early pregnancy were assessed at 18 weeks gestation. Questionnaires assessed 42 SLEs (see Table S1, available online). Respondents were asked whether each event had occurred ‘since you became pregnant’ and, if so, how severely the respondent was affected by it (‘0’- did not happen or ‘1’-yes but did not affect me’ to 4-‘affected me greatly’). SLEs in late pregnancy and the postnatal period were collected at eight weeks postpartum using the stem ‘have any of these occurred since the middle of your pregnancy’.

Scores for each event were summed to create a total score (possible range 0-168) at each time point.

Outcomes

Primary outcome. At age 17/18 (median age: 17 years, 9 months) offspring completed a computerized version of the *Clinical Interview Schedule-Revised* (CIS-R).[21] The computerized version is considered as reliable as an interview conducted by a trained clinician.[22] Both a continuous symptom score and binary variable indicating a primary diagnosis of major depression in accordance with ICD-10 criteria were considered as primary outcomes.

Secondary outcome. Offspring depressive symptoms were also assessed using 13 self-report items from the *Short Mood and Feelings Questionnaire* (SMFQ).[23] Participants completed the SMFQ at six time points (ages 10/11, 12/13, 13/14, 16/17, 17/18, and 18/19), either on a computer terminal during a clinic visit or by answering the same questions in a postal questionnaire (ages 16/17 and 18/19). Participants rated each item on a three-point scale (0-'not true', 1-'sometimes true', 2-'true'). Item scores were summed to create a total depressive symptoms score. The scale demonstrated good internal consistency across all time points, with Cronbach's alpha values ranging from .80 to .91.

Covariates

Several sociodemographic variables were identified as potential confounders: gender, maternal age, social class (highest of both parents, based on occupation, from 1-'working class' to 3-'professional'), child ethnicity (caucasian vs. non-caucasian), and maternal education (self reported). Education up to age 16 (compulsory education only) was categorized as low education and post 16 as high education.[24]

We also included maternal history of severe depression prior to pregnancy (self-reported at 12 weeks gestation using the prompt 'Have you ever had any of the following problems: severe depression?'), maternal prenatal smoking (self-reported, any versus none) and alcohol use (self-reported, at least once per week vs. less than once per week) as covariates in the model.

We also considered maternal prenatal depression and anxiety as covariates. Depression was assessed at 18 and 32 weeks gestation using the Edinburgh Postnatal Depression Scale (EPDS). Mothers were categorized into 'high' vs. 'low' prenatal depression based on the mean of their 18 and 32 week gestation EPDS scores (>12 vs. ≤12).[13,25] Anxiety was assessed using the Crown-Crisp anxiety subscale. As there is no established cutoff for this measure, mothers were considered anxious if the mean of their scores at 18 and 32 weeks gestation was in the top 15%.[10] Finally, we considered mothers' SLEs at eight months postpartum and maternal depressive symptoms at eight years postpartum. The weighted life events scale was dichotomized at the top quartile for analyses. As with prenatal depression, mothers were considered depressed at eight years postpartum if their EPDS score was above 12.

Statistical analysis

Linear and logistic regression were used to predict offspring CIS-R depressive symptoms and depression diagnosis, respectively, at age 17/18 from weighted prenatal SLE scores. Confounders were added to the model in steps. Given literature suggesting gender differences in the associations between prenatal stress and offspring mental health, we also considered interactions between SLEs and offspring sex in the prediction of depression.[26] Latent Class Growth Modeling (LCGM) was used to identify distinct longitudinal trajectories of depressive symptoms using SMFQ scores from age 10/11 to 18/19. We used the PROC TRAJ application,

which allows for irregular spacing of measurements, as was the case in this study.[27,28] The final model was selected based on maximizing the Bayesian Information Criterion (BIC) while ensuring average posterior probabilities in each class remained above .70. [29]

Multinomial logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for membership in trajectories of depressive symptoms, with the lowest trajectory as the reference group. To facilitate interpretation of odds ratios in multinomial logistic regressions, weighted SLE scores at each time point were collapsed into quartiles, with the lowest quartile as the reference category.[19] As above, we also considered interactions between stressful life events and offspring sex in the prediction of depression trajectories.

Missing data on outcomes and confounders was imputed using fully conditional specification. Five imputed datasets were created and estimates were pooled. Results were similar in the complete case sample and the imputed sample; results for both samples are presented below for comparison.

Analyses were conducted using SPSS version 22 and SAS® version 9.3.[30,31]

Sensitivity Analysis

In addition to the primary analysis, we conducted an identical post-hoc sensitivity analysis with additional covariates that had higher rates of missing data: paternal age, paternal history of depression, paternal education, maternal prenatal antidepressant use, single parenthood and childhood stressful events. Paternal age was a categorical variable operationalized into 5-year intervals until age 50+. Paternal history of depression was self-reported, similar to maternal history of depression. Paternal education was operationalized analogously to maternal education. Maternal antidepressant use was self-reported at eight weeks postpartum. Single motherhood was

assessed at 8 months postpartum by the question “Does your partner live with you?” Frequency of childhood SLEs were mother reported annually from age one until six, and dichotomized at the 75th percentile.

RESULTS

The prevalence of depression at age 17/18 was 7.7% (Table 1). SLE scores ranged from 0 to 61, with a median of 6. The most commonly reported individual life events were prenatal tests for abnormality (53.4%), arguments with a partner (50.2%), and income reductions (20.8%). The events rated as most severe were death of a child (average severity rating among mothers who experienced the event: 3.38 on a four-point scale), attempted abortion (3.28), and miscarriage scare (3.22).

Prediction of depression at age 17/18

An increase of one unit on the maternal SLE score during gestation was associated with increased offspring depressive symptoms (β=0.07, p<.01) and major depression at age 17/18 (OR:1.03 95%CI:1.01,1.05), after adjusting for all covariates (Table 2). This corresponds to a 12.6% increased risk of internalizing disorders if an event occurred and greatly affected the mother (4 point increase).

Results using the imputed data were similar. A one-unit increase in maternal SLE score was associated with increased depressive symptoms (β=0.17, p<.05) and higher risk of depression (OR:1.02, 95%CI:1.01,1.04) for offspring at age 17/18, corresponding to a 6.1% increased risk of depression for experiencing an additional event that greatly affected the mother. No interactions between sex and maternal SLE score on depression were significant.

Trajectory analysis

Using the criteria identified above, three-, four-, and five- group trajectory models were compared. The four-group model showed improved BIC over the three-group model (-89975.29

vs -90432.78). Though the BIC for the five-group model was improved (-89806.36), the average posterior probabilities in each class did not meet the established minimum criteria of .70. Average posterior probabilities for the four-group model were good, ranging from 0.70-0.81. Consequently, the four-group model was chosen as the best fitting model.

Trajectories of depressive symptoms are presented in Figure 1. The first group showed a pattern of consistently low MFQ scores. This group, labeled 'stable low' depressive symptoms, comprised 61.8% of the sample (5663 adolescents). The second group, labeled 'stable moderate', showed a pattern of depressive symptoms with a higher intercept than the 'stable low' group, which increased modestly over time. This group consisted of 2455 adolescents (26.8% of the sample). The third group ('moderate increasing') consisted of 547 adolescents (6% of the sample) whose depressive symptoms were moderate at age 10/11 and 12/13, and increased dramatically over time thereafter. The final group consisted of 501 youth (5.5% of the sample) whose depressive symptoms began relatively high, increased until age 16.5, then decreased (remaining relatively high) until age 18/19. This group was labeled 'consistently high' depressive symptoms.

Sample characteristics in each trajectory are presented in Table 3.

Prediction of trajectories of depressive symptoms

Results of the multinomial logistic regressions are presented in Table 4. In the crude model, high maternal stress (4^{th} quartile SLEs) during early pregnancy was predictive of membership in all three trajectories characterized by elevated symptoms of depression (compared to the stable low trajectory). Adjusting for all confounders, offspring of mothers in the highest quartile of SLEs

had 1.7 times greater odds of membership in the trajectory characterized by consistently high levels of depressive symptoms (95%CI:1.07,2.69) compared to the lowest quartile.

Results using the imputed data were comparable. In the adjusted model, offspring of mothers in the highest quartile of SLEs had greater odds of belonging to trajectories characterized by consistently high (OR:1.49, 95%CI:1.04,2.14) or increasing depressive symptoms (OR:1.45, 95%CI: 1.04,2.01). No interactions between sex and maternal SLE quartile on depressive symptom trajectories were significant.

Sensitivity Analysis

Inclusion of additional covariates in the post-hoc sensitivity analysis reduced the sample size by 30% in the complete case analysis due to missing data, and significantly increased the degree of imputation in the imputed samples. In these models, an increase of one unit on the maternal SLE score during gestation was associated with increased offspring depressive symptoms (complete case analysis β=0.06, p=0.02; imputed sample β=0.18, p=0.049) and major depression at age 17/18 (complete case analysis OR:1.04 95%CI:1.00,1.07; imputed sample OR:1.02 95%CI:1.00,1.04). In these models, the association between high prenatal maternal stress and trajectories of depressive symptoms was attenuated.

DISCUSSION

In this prospective study of 10,569 parents and offspring, we demonstrate that offspring of mothers exposed to stressful events during early pregnancy may be at increased risk of depression and elevated depressive symptoms at age 17/18, even after maternal depression, anxiety, and other known prenatal and early life risk factors were taken into account. This increased risk persisted after adjusting for stress in the late prenatal/early postnatal period, suggesting that exposure to stress in early pregnancy may be a specific risk factor for offspring depression.

These results provide support for the fetal programming hypothesis for depressive symptoms. There is considerable evidence that maternal exposure to stress in utero may lead to abnormal development of the HPA axis, with long-term consequences for offspring mental health and behavior.[32,33] Our results are in line with evidence from animal studies and support earlier reports of associations between prenatal anxiety and stress and offspring behavioral and emotional disorder in humans.[3–5,8–13]

Of note, increasing prenatal exposure to stressful life events was linearly associated with depressive symptoms in adolescence, suggesting a dose-response relationship, lending plausibility to the notion that prenatal stress may be causally linked to offspring depression. Several authors have speculated as to the mechanisms underlying such a link. Maternal stress increases circulating glucocorticoids, which may pass through the placental barrier to the fetus.[34] Exposure to high levels of glucocorticoids may affect the developing HPA axis, rendering it hyperresponsive to stress.[35] Recent studies suggest that prenatal maternal stress may also disrupt placental functioning, resulting in greater fetal exposure to cortisol. For example, the barrier enzyme 11βHSD2, which converts maternal cortisol to inactive cortisone, may be down

regulated under stressful conditions.[36,37] Prenatal maternal distress has also been linked to elevated inflammation, which may in turn disrupt brain development.[38] Exposure to prenatal stress may also lead to maternal anxiety and depression, which may impinge on maternal care and nurturing.[35] Though the present study did not consider differences in parenting, the associations persisted after adjusting for maternal anxiety and depression, suggesting that these mood disturbances do not fully account for the link between prenatal stress and offspring depression.

Early prenatal exposure to stress was also associated with membership in different trajectories of depressive symptoms across adolescence. Our results provided evidence for four distinct trajectories of depressive symptoms from age 10/11 to 18/19. These trajectories are comparable to those found in other studies of depressive symptoms at similar ages.[39] Early prenatal exposure to stress predicted membership in the trajectory characterized by consistently elevated depressive symptoms, as early as age 10/11. This result lends further support to the fetal programming hypothesis. If maternal stress during pregnancy alters HPA axis development in the offspring, rendering it hyperresponsive to stress, we might expect the effects of such hyperresponsiveness to be observable early in life. Indeed, previous studies have reported associations between maternal cortisol and offspring temperament as early as infancy.[40] Similar results have also been observed in a study of the association between low birth weight and trajectories of depressive symptoms from adolescence to adulthood; low birth weight predicted early-onset depressive symptoms but not adult-onset symptoms.[41]

Notably, later SLEs were also associated with depressive symptoms, and different patterns of symptoms over time. However, because stressful events in the latter half of pregnancy were assessed at eight weeks postpartum, the effect of late pregnancy stress cannot be disentangled

from stress occurring in the early postnatal period. Maternal stress, anxiety, and depression in the postpartum period have been associated with offspring depression and emotional problems.[10,13,42] Theory and findings regarding the timing of exposure to prenatal stress have been mixed.[43] Some authors have argued that due to blunting of the maternal HPA axis response in later pregnancy, exposure to stress is most detrimental to development in early pregnancy.[12,43] In contrast, other work suggests that whereas first trimester stress impinges on the development of major organs, stress in later pregnancy may exert a greater effect on neurobehavioral development.[10,43] Discrepancies in findings between studies may be due in part to the heterogeneity of the outcomes assessed, as well to variations in the age of the offspring at follow-up. It is possible that maternal stress has different timing-specific effects on the development of different specific mental health outcomes. Our results suggest that stress in the first 18 weeks of pregnancy may confer particular vulnerability to depression. However, it is possible that mothers' reactions to stressors early in pregnancy continue to exert influence on prenatal development in later pregnancy, when the fetal brain is undergoing rapid development.

Results of the study should be interpreted in light of its limitations. Mothers' ratings of the severity of SLEs may have been influenced by stress coping factors such as chronic anxiety, depression, or neuroticism. To test this possibility, we calculated the mean severity for each event among those that experienced the event (reported 1-4), and assigned this score to each individual who had reported experiencing that event. In this way, we equalized the severity and coping skills of each mother to a particular event. No substantial changes were noted in the strengths of associations between SLEs and depression status, depressive symptoms, or trajectories, lending confidence to the original findings. Moreover, by adjusting for covariates such as maternal history of depression, prenatal depression and anxiety, and SLEs in the

postnatal period, we can be more confident that the measure of SLEs used reflects recent onset stressors limited to the early prenatal period.

As a longitudinal cohort study, ALSPAC was subject to considerable attrition over time. However, the similarity of results for complete case and imputed samples lends confidence that the results were not unduly influenced by missing data. Moreover, other authors working with the ALSPAC cohort have reported that although dropout was nonrandom, results of regression models predicting offspring behavior disorders and depression were nonetheless negligibly influenced by attrition.[13,44] However, the complete sample has been shown to represent participants from higher SES backgrounds than the UK population, and results may therefore not be generalizable to other populations.[45]

Lastly, we were unable to fully distinguish between acute versus chronic stressors, a factor thought to moderate detrimental effects in offspring.[46] However, by asking about stressful events that occurred during pregnancy and controlling for depression and anxiety before pregnancy and after birth, we target recent events and control for potentially chronic mental health symptoms in the mother related to those events.

These limitations were offset by several noteworthy strengths. First, we used a large national birth cohort sample with a follow-up period of almost 20 years. Second, stressful life events and many other potential confounding factors were assessed during pregnancy, rather than by retrospective report. Finally, offspring depression at age 17/18 was measured using a reliable standardized interview.

These findings highlight the potential impact of maternal stress during pregnancy on offspring mental health. Though certain stressful life events are unavoidable, helping pregnant women cope adaptively with such stressors may lessen the extent of their impact on fetal development.

There is also some evidence to suggest that enrichment later in life may help counteract the effects of prenatal stress on HPA axis reactivity.[47] Offspring of mothers exposed to recent stress during pregnancy may benefit from intervention in the form of enriched care in early life. Such interventions may be particularly important as mothers who have experienced severe stress may be at risk of depression and dysfunctional mother-child interactions.[42]

REFERENCES

1. Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis. *Neurosci Biobehav Rev*. 2010;35(1):17-22.
2. Phillips DI, Jones A. Fetal programming of autonomic and HPA function: do people who were small babies have enhanced stress responses? *J Physiol*. 2006;572(Pt 1):45-50.
3. Weinstock M. The long-term behavioural consequences of prenatal stress. *Neurosci Biobehav Rev*. 2008;32(6):1073-1086.
4. Drago F, Di Leo F, Giardina L. Prenatal stress induces body weight deficit and behavioural alterations in rats: the effect of diazepam. *Eur Neuropsychopharmacol*. 1999;9(3):239-245.
5. Coe CL, Kramer M, Czeh B, et al. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. *Biol Psychiatry*. 2003;54(10):1025-1034.
6. Colman I, Ataullahjan A, Naicker K, Van Lieshout RJ. Birth weight, stress, and symptoms of depression in adolescence: evidence of fetal programming in a national Canadian cohort. *Can J Psychiatry*. 2012;57(7):422-428.
7. Wojcik W, Lee W, Colman I, Hardy R, Hotopf M. Foetal origins of depression? A systematic review and meta-analysis of low birth weight and later depression. *Psychol Med*. 2013;43(1):1-12.
8. O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry Allied Discip*. 2003;44(7):1025-1036.
9. O'connor TG, Heron J, Glover V, Team AS. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *J Am Acad Child Adolesc Psychiatry*. 2002;41(12):1470-1477.
10. O'Connor TG, Heron J, Golding J, Beveridge M, Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *Br J Psychiatry*. 2002;180:502-508.
11. Gutteling BM, de Weerth C, Willemsen-Swinkels SHN, et al. The effects of prenatal stress on temperament and problem behavior of 27-month-old toddlers. *Eur Child Adolesc Psychiatry*. 2005;14(1):41-51.
12. Van den Bergh BRH, Marcoen a. High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8-and 9-year-olds. *Child Dev*. 2004;75(4):1085-1097.

13. Pearson RM, Evans J, Kounali D, et al. Maternal Depression During Pregnancy and the Postnatal Period Risks and Possible Mechanisms for Offspring Depression at Age 18 Years. *JAMA Psychiatry*. 2013;70(12):1312-1319.

14. Selten JP, van der Graaf Y, van Duursen R, Gispen-de Wied CC, Kahn RS. Psychotic illness after prenatal exposure to the 1953 Dutch Flood Disaster. *Schizophr Res*. 1999;35(3):243-245.

15. Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944-1945. *Arch Gen Psychiatry*. 1992;49(12):983-988.

16. Meijer A. Child psychiatric sequelae of maternal war stress. *Acta Psychiatr Scand*. 1985;72(6):505-511.

17. Huttunen MO, Niskanen P. Prenatal Loss of Father and Psychiatric-Disorders. *Arch Gen Psychiatry*. 1978;35(4):429-431.

18. Khashan AS, Abel KM, McNamee R, et al. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Arch Gen Psychiatry*. 2008;65(2):146-152.

19. Dorrington S, Zammit S, Asher L, Evans J, Heron J, Lewis G. Perinatal maternal life events and psychotic experiences in children at twelve years in a birth cohort study. *Schizophr Res*. 2014;152(1):158-163.

20. Brown AS, van Os J, Driessens C, Hoek HW, Susser ES. Further evidence of relation between prenatal famine and major affective disorder. *Am J Psychiatry*. 2000;157(2):190-195.

21. Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring Psychiatric-Disorder in the Community - a Standardized Assessment for Use by Lay Interviewers. *Psychol Med*. 1992;22(2):465-486.

22. Patton GC, Coffey C, Posterino M, Carlin JB, Wolfe R, Bowes G. A computerised screening instrument for adolescent depression: population-based validation and application to a two-phase case-control study. *Soc Psychiatry Psychiatr Epidemiol*. 1999;34(3):166-172.

23. Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D. Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *Int J Methods Psychiatr Res*. 1995;5(4):237-249.

24. Dunn J, Deater-Deckard K, Pickering K, O'Connor TG, Golding J. Children's adjustment and prosocial behaviour in step-, single-parent, and non-stepfamily settings: findings from a community study. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and

Childhood. *J Child Psychol Psychiatry Allied Discip*. 1998;39(8):1083-1095.

25. Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. *BMJ*. 2001;323(7307):257-260.

26. Weinstock M. Gender differences in the effects of prenatal stress on brain development and behaviour. *Neurochem Res*. 2007;32(10):1730-1740.

27. Nagin DS. Analyzing developmental trajectories: a semiparametric, group-based approach. *Psychol Methods*. 1999;4(2):139-157.

28. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. *Sociol Methods Res*. 2007;35(4):542-571.

29. Andruff H, Carraro N, Thompson A, Gaudreau P, Louvet B. Latent Class Growth Modelling: A Tutorial. *Tutor Quant Methods Psychol*. 2009;5:11-24.

30. IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

31. SAS Institute Inc. 2011. Base SAS® 9.3. Cary, NC: SAS Institute Inc.

32. Mulder EJH, de Medina PGR, Huizink AC, Van den Bergh BRH, Buitelaar JK, Visser GHA. Prenatal maternal stress: effects on pregnancy and the (unborn) child. *Early Hum Dev*. 2002;70(1-2):3-14.

33. Weinstock M. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Prog Neurobiol*. 2001;65(5):427-451.

34. Gitau R, Cameron A, Fisk NM, Glover V. Fetal exposure to maternal cortisol. *Lancet*. 1998;352(9129):707-708.

35. Maccari S, Darnaudery M, Morley-Fletcher S, Zuena AR, Cinque C, Van Reeth O. Prenatal stress and long-term consequences: implications of glucocorticoid hormones. *Neurosci Biobehav Rev*. 2003;27(1-2):119-127.

36. Cottrell EC, Seckl JR, Holmes MC, Wyrwoll CS. Foetal and placental 11beta-HSD2: a hub for developmental programming. *Acta Physiol*. 2014;210(2):288-295.

37. O'Donnell KJ, Bugge Jensen A, Freeman L, Khalife N, O'Connor TG, Glover V. Maternal prenatal anxiety and downregulation of placental 11beta-HSD2. *Psychoneuroendocrinology*. 2012;37(6):818-826.

38. O'Connor TG, Monk C, Fitelson EM. Practitioner review: maternal mood in pregnancy and child development--implications for child psychology and psychiatry. *J Child Psychol Psychiatry Allied Discip*. 2014;55(2):99-111.

39. Brendgen M, Wanner B, Morin AJS, Vitaro F. Relations with parents and with peers, temperament, and trajectories of depressed mood during early adolescence. *J Abnorm Child Psychol*. 2005;33(5):579-594.

40. Davis EP, Glynn LM, Schetter CD, Hobel C, Chicz-Demet A, Sandman CA. Prenatal exposure to maternal depression and cortisol influences infant temperament. *J Am Acad Child Adolesc Psychiatry*. 2007;46(6):737-746.

41. Colman I, Ploubidis GB, Wadsworth ME, Jones PB, Croudace TJ. A longitudinal typology of symptoms of depression and anxiety over the life course. *Biol Psychiatry*. 2007;62(11):1265-1271.

42. Essex MJ, Klein MH, Cho E, Kalin NH. Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behavior. *Biol Psychiatry*. 2002;52(8):776-784.

43. Austin MP, Leader LR, Reilly N. Prenatal stress, the hypothalamic-pituitary-adrenal axis, and fetal and infant neurobehaviour. *Early Hum Dev*. 2005;81(11):917-926.

44. Wolke D, Waylen A, Samara M, et al. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *Br J Psychiatry*. 2009;195(3):249-256.

45. Boyd A, Golding J, Macleod J, et al. Cohort profile: The "Children of the 90s"-The index offspring of the avon longitudinal study of parents and children. *Int J Epidemiol*. 2013;42(1):111-127.

46. Borders AEB, Grobman W a, Amsden LB, Holl JL. Chronic stress and low birth weight neonates in a low-income population of women. *Obstet Gynecol*. 2007;109(2 Pt 1):331-338.

47. Morley-Fletcher S, Rea M, Maccari S, Laviola G. Environmental enrichment during adolescence reverses the effects of prenatal stress on play behaviour and HPA axis reactivity in rats. *Eur J Neurosci*. 2003;18(12):3367-3374.

TABLES

Table 1. Sample characteristics by *Clinical Interview Schedule-Revised* (CIS-R) depression status at age 17/18 (complete cases)

	Overall	CIS-R diagnosis of major depression	Non depressed	*p*-value (χ^2 test)
	n = 2884	n = 206 (7.1%)	n = 2,678 (92.7%)	
Sex (female)	1599 (55.4%)	154 (74.8%)	1445 (54.0%)	< .001
Maternal education (beyond age 16)	1476 (51.2%)	91 (44.2%)	1385 (51.7%)	< 0.05
Child ethnicity (nonwhite)	92 (3.2%)	6 (2.9%)	86 (3.2%)	0.81
Maternal teenage status	28 (1.0%)	7 (3.4%)	21 (0.8%)	< .001
Social class (working class)	1948 (67.5%)	133 (64.6%)	1815 (67.8%)	0.45
Maternal history of depression	160 (5.5%)	14 (6.8%)	146 (5.5%)	0.42
Prenatal smoking (any reported)	281 (9.7%)	35 (17.0%)	246 (9.2%)	< .001
Prenatal alcohol use (at least once per week)	428 (14.8%)	36 (17.5%)	392 (14.6%)	0.27
Prenatal depression	193 (6.7%)	16 (7.8%)	177 (6.6%)	0.52
Prenatal anxiety	314 (10.9%)	28 (13.6%)	286 (10.7%)	0.20
Maternal SLEs at 8mo postpartum (4^{th} quartile)	676 (23.4%)	60 (29.1%)	616 (21.4%)	< .05
Maternal depression- 8 years postpartum	320 (11.1%)	27 (13.1%)	293 (10.9%)	0.34

Table 2. Results of linear and logistic regression models predicting offspring *Short Mood and Feelings Questionnaire* (SMFQ) depressive symptoms and *Clinical Interview Schedule-Revised* (CIS-R) depression status from stressful life events during early pregnancy, in complete and imputed sample.

	SMFQ Depressive Symptoms			CIS-R Depression Status					
	Crude Model	Complete Cases	Imputed Sample	Crude model		Complete Cases		Imputed Sample	
	β	β	β	OR	95% CI	OR	95% CI	OR	95% CI
Weighted SLEs – 18 weeks gestation	**0.11*****	**0.07****	**0.17***	1.03	1.01, 1.05	**1.03**	1.01, 1.06	**1.02**	1.01, 1.04
Weighted SLEs – 8 weeks postpartum		**0.05***	**0.17***			0.99	0.97, 1.02	1.00	0.98, 1.02
Sex (female)		**0.17*****	**0.72*****			**2.58**	1.86, 3.58	**3.06**	2.04, 4.58
Maternal education (beyond age 16)		- 0.02	0.02			0.80	0.59, 1.08	1.17	0.69, 1.99
Maternal history of depression		0.01	**0.13***			0.99	0.54, 1.80	**1.43**	1.01, 2.03
Ethnicity (non-caucasian)		- 0.02	- 0.06			0.79	0.34, 1.88	1.02	0.30, 3.45
Teenage status of mother		0.03	**0.06***			**3.71**	1.48, 9.33	**3.12**	1.70, 5.75
Social class (professional)		- 0.03	0.00			0.51	0.18, 1.46	0.56	0.13, 2.49
Prenatal Smoking		**0.07*****	**0.22***			**1.69**	1.12, 2.56	**1.60**	1.07, 2.39
Prenatal alcohol use		0.01	- 0.04			1.24	0.85, 1.83	1.17	0.90, 1.52
Prenatal depression		- 0.01	0.03			0.81	0.42, 1.57	1.01	0.70, 1.45
Prenatal anxiety		0.02	0.07			1.15	0.68, 1.92	1.01	0.65, 1.58
SLEs at 8 mo postpartum		0.04	0.12			1.16	0.80, 1.67	0.95	0.67, 1.33
Maternal depression at 8 years postpartum		0.02	0.09			1.02	0.64, 1.61	1.11	0.60, 2.03

*** p < .001, ** p< .01, * p< .05, **bold** text indicates statistical significance at p<0.05

Table 3. Sample characteristics, by trajectory of *Short Mood and Feelings Questionnaire* depressive symptoms.

	Overall n = 9166	Stable Low n = 5663 (61.8%)	Stable Moderate n = 2455 (26.8%)	Moderate Increasing n = 547 (6%)	Consistently High n = 501 (5.5%)	*p*-value (χ^2 test)
Sex (female)	4742 (51.7%)	2517 (44.4%)	1461 (59.5%)	409 (74.9%)	355 (71.0%)	< .001
Maternal education (beyond age 16)	3397 (41.1%)	2101 (41.1%)	949 (43.1%)	174 (35%)	173 (38.3%)	< .01
Maternal history of depression	634 (7.7%)	339 (6.6%)	194 (8.7%)	46 (9.3%)	55 (12.1%)	< .001
Child ethnicity (nonwhite)	344 (4.2%)	205 (4.1%)	96 (4.4%)	27 (5.5%)	16 (3.7%)	0.41
Maternal teenage status	206 (2.4%)	120 (2.2%)	48 (2.1%)	15 (2.9%)	23 (4.8%)	< .01
Social class (working class)	4580 (60.8%)	2836 (60.8%)	1255 (62%)	268 (59.8%)	221 (54.8%)	< .05
Prenatal smoking (any)	1263 (15%)	703 (13.5%)	346 (15.3%)	98 (19.5%)	116 (25.1%)	< .001
Prenatal alcohol use (at least once per week)	1290 (15.4%)	800 (15.4%)	346 (15.4%)	75 (15.0%)	69 (14.9%)	0.99
Prenatal depression	863 (10.5%)	456 (9%)	268 (12.2%)	59 (12.2%)	80 (18.3%)	< .001
Prenatal anxiety	1234 (15%)	645 (12.7%)	394 (17.8%)	90 (18.5%)	105 (23.8%)	< .001
Maternal SLEs at 8mo postpartum (4^{th} quartile)	1977 (24.8%)	1076 (21.9%)	618 (28.9%)	135 (28.6%)	148 (24.1%)	< .001
Maternal depression-8 years postpartum	861 (12.4%)	452 (10.6%)	275 (14.8%)	63 (14.5%)	71 (18.7%)	< .001

Table 4. Results of multinomial logistic regression predicting offspring *Short Mood and Feelings Questionnaire* depressive symptom trajectory membership from mothers' SLEs during early pregnancy (lowest quartile is the reference group), in full and imputed samples.

	Stable Moderate		Moderate Increasing		Consistently High	
	OR	95% CI	OR	95% CI	OR	95% CI
Crude model – complete cases						
4th quartile early prenatal SLEs	**1.52**	1.30, 1.78	**1.85**	1.38, 2.48	**2.81**	2.04, 3.87
3rd quartile early prenatal SLEs	**1.29**	1.11, 1.49	1.30	0.97, 1.75	**1.75**	1.26, 2.42
2nd quartile early prenatal SLEs	**1.17**	1.01, 1.35	1.18	0.88, 1.57	1.37	0.98, 1.90
Adjusted model[a] – complete cases						
4th quartile early prenatal SLEs	1.09	0.87 1.36	1.27	0.84, 1.92	**1.72**	1.09, 2.71
3rd quartile early prenatal SLEs	1.09	0.90, 1.32	1.24	0.86, 1.78	1.39	0.91, 2.11
2nd quartile early prenatal SLEs	1.10	0.92, 1.32	1.15	0.82, 1.63	1.28	0.86, 1.91
4th quartile later pregnancy/ postpartum SLEs	**1.39**	1.10, 1.75	1.48	0.99, 2.21	1.31	0.83, 2.07
Adjusted model[a] – imputed sample (pooled)						
4th quartile early prenatal SLEs	1.07	0.86, 1.32	**1.45**	1.04, 2.01	**1.49**	1.04, 2.14
3rd quartile early prenatal SLEs	1.11	0.93, 1.32	1.24	0.92, 1.67	1.33	0.85, 2.07
2nd quartile early prenatal SLEs	1.07	0.92, 1.23	1.16	0.85, 1.58	1.19	0.85, 1.65
4th quartile later pregnancy/ postpartum SLEs	**1.32**	1.03, 1.69	1.37	0.94, 2.00	1.41	1.00, 1.98

[a] model adjusted for gender, ethnicity, maternal teen status, maternal education, maternal history of depression, prenatal smoking and alcohol use, prenatal depression and anxiety, high maternal stress at 8 months postpartum and maternal depression at 8 years postpartum.

bold text indicates statistical significance at $p<0.05$

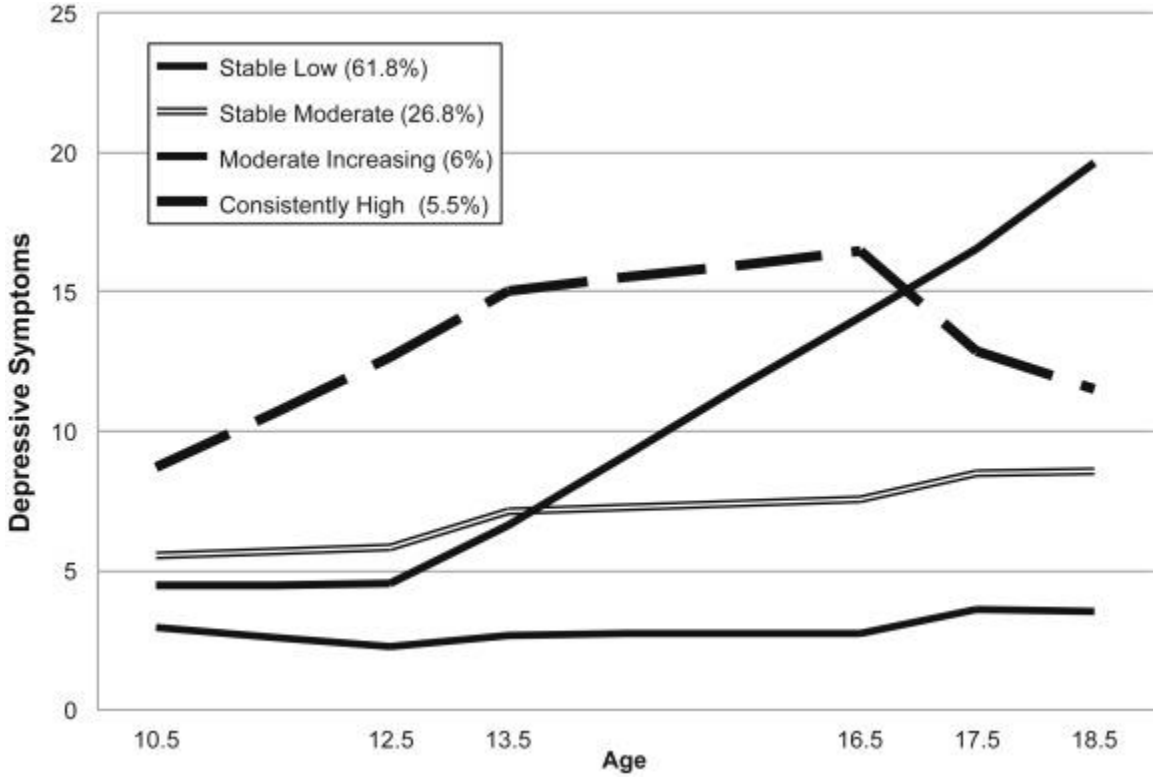
Supplemental Table 1. Complete list of life events reported during pregnancy.

Stressful Life Event	Prevalence (%)
1. Your partner died	0.1
2. One of your children died	0.1
3. A friend or relative died	10.1
4. One of your children was ill	12.8
5. Your partner was ill	9.9
6. A friend or relative was ill	14.9
7. You were admitted to hospital	2.9
8. You were in trouble with the law	0.6
9. You were divorced	0.8
10. You found out that your partner didn't want your child	2.5
11. You were very ill	7.1
12. Your partner lost his job	5.1
13. Your partner had problems at work	15.8
14. You had problems at work	11.2
15. You lost your job	2.8
16. Your partner went away	6.4
17. Your partner was in trouble with the law	2.0
18. You and your partner separated	3.0
19. Your income was reduced	16.2
20. You argued with your partner	29.3
21. You had arguments with your family or friends	14.0
22. You moved house	8.0
23. Your partner hurt you physically	1.3
24. You became homeless	1.1
25. You had major financial problems	10.7
26. You got married	2.6

27. Your partner hurt your children physically	0.1
28. You attempted suicide	0.1
29. You were convicted of an offence	0.2
30. You were bleeding and thought you might miscarry	13.0
31. You started a new job	3.7
32. You had a test to see if your baby was abnormal	41.6
33. You had a result on a test that suggested your baby might not be normal	3.0
34. You were told you were going to have twins	2.7
35. You heard that something that had happened might be harmful to the baby	6.7
36. You tried to have an abortion	0.7
37. You took an examination	4.5
38. Your partner was emotionally cruel to you	4.7
39. Your partner was emotionally cruel to your children	0.5
40. Your house or car was burgled	4.1
41. You had an accident	3.0
42. Other	9.2

Figure titles

Figure 1. Trajectories of *Short Mood and Feelings Questionnaire* depressive symptoms across six time points from age 10/11 to 18/19.



Supplemental Figure. Sample inclusion and exclusion