Effects of prenatal and postnatal depression, and maternal stroking, at the glucocorticoid receptor gene

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In animal models, prenatal and postnatal stress is associated with elevated hypothalamic–pituitary axis (HPA) reactivity mediated via altered glucocorticoid receptor (GR) gene expression. Postnatal tactile stimulation is associated with reduced HPA reactivity mediated via increased GR gene expression. In this first study in humans to examine the joint effects of prenatal and postnatal environmental exposures, we report that GR gene (NR3C1) 1-F promoter methylation in infants is elevated in the presence of increased maternal postnatal depression following low prenatal depression, and that this effect is reversed by self-reported stroking of the infants by their mothers over the first weeks of life.

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INTRODUCTION

In animal models, prenatal and postnatal stress cause long-term elevations in hypothalamic–pituitary axis (HPA) reactivity and anxiety-like behaviors. These effects are mediated via altered glucocorticoid receptor (GR) gene expression. In rodents, maternal licking and grooming over the first days of life cause reduced HPA-axis reactivity and anxiety-like behaviors mediated via increased GR expression accounted for, at least in part, by demethylation at exon 1–7 promoter of the rat GR gene (Nr3c1) in the hippocampus of the offspring. These epigenetic changes emerge over the first week of life and persist into adulthood. Epigenetic modifications are thought to link early-life stress to later susceptibility to behavioral disorders through interference with the development and functioning of the HPA-axis early in life. The epigenetic process of DNA methylation involves the addition of methyl groups to CpG dinucleotides in gene regulatory regions that associate with repression of gene expression. Translation into humans would have far-reaching consequences for our understanding of the role of early environmental stressors, with implications for health and social policy. Findings consistent with fetal programming of HPA-axis regulation have been reported in humans. Maternal anxiety and depression during pregnancy predict childhood behavior problems after controlling for postnatal environmental exposure, and prenatal maternal anxiety predicts persistence of behavior problems from childhood to adolescence. Prenatal maternal depression predicts infant temperament, negative emotionality and maternal cortisol during pregnancy predicts infant cortisol reactivity to a stressor. Animal findings of the epigenetic effects of early-life stress have been validated in humans in a study reporting elevated NR3C1 1-F promoter methylation and reduced GR expression in postmortem hippocampal tissue of suicide completers who were abused during childhood, when compared with non-abused. Other studies using peripheral DNA, from blood or saliva of infants and adolescents, have shown increased levels of NR3C1 methylation in response to perinatal stress and abuse or neglect during childhood. Many further report enduring DNA methylation changes in adulthood following stress or traumatic events such as abuse or neglect in childhood. Several clinical studies examining leukocytes have reported elevated methylation of the homologous human NR3C1 1-F promoter (homologous to the rat 1–7 promoter) at a specific CpG (CpG unit 22,23, Figure 1) associated with prenatal maternal depression and childhood stress. Effects of postnatal maternal behaviors reported in animal models have not so far been translated into humans. The postnatal maternal licking and grooming effects on rodent GR expression, Nr3c1 1–7 promoter region demethylation, improved HPA-axis regulation and reduced anxiety behaviors. are caused by tactile stimulation. We therefore asked whether, in humans, maternal stroking has the effect that would be predicted from the animal work, that is, does it reverse prenatal stress effects? Using a self-report measure on two occasions, we asked mothers participating in the longitudinal Wirral Child Health and Development Study, how often they stroked their infants when they were 5 and 9 weeks old. We found that associations of prenatal depression with vagal reactivity and temperament at 29 weeks of age were both modified by maternal stroking over the first weeks of life. The significant statistical interaction was that increasing prenatal depression was associated with decreasing vagal reactivity, which is likely to be associated later in life with poorer emotion regulation, only in the infants of low-stroking mothers. Similarly the association between prenatal depression and increasing negative emotionality, as reported by mothers in a standard measure of temperament, was also seen only in the infants of low-stroking mothers. Reporting from the same sample, we have recently shown that maternal stroking interacts with prenatal anxiety to predict child emotional problems at 2.5 years—the association between maternal anxiety and child emotional problems was evident only in the children of low-stroking mothers. These are the first findings in humans of an enduring effect of maternal stroking on the basis of predictions from animal models. No previous studies have investigated whether NR3C1

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methylation associated with maternal depression is modified by maternal stroking.

In the case of maternal depression, prenatal and postnatal levels are highly correlated, and each has to be accounted for in predicting DNA methylation. Strikingly, animal studies have not yet looked at the joint effects of the human condition by examining the joint effects of pre- and postnatal stress, and so there is no firm basis from which to predict in humans. We, therefore, examined whether each of pre- or postnatal depression have effects on infant NR3C1 1-F promoter DNA methylation at CpG unit 22 and 23, or that they interact to give distinct outcomes. We also investigated whether effects of maternal depression are reversed by maternal stroking.

MATERIALS AND METHODS

Design

The participants were members of the Wirral Child Health and Development Study, a prospective epidemiological longitudinal study of prenatal and infancy origins of conduct disorders. This uses a two stage stratified design in which a larger general population sample of first-time mothers who booked for antenatal care at 18 weeks gestation at a clinic was administered by the Wirral University Teaching Hospital which is from consecutive first-time mothers who booked for antenatal care at 12 weeks gestation between 12/02/2007 and 29/10/2008. The booking clinic was administered by the Wirral University Teaching Hospital which is the sole provider of universal antenatal care on the Wirral Peninsula. Socioeconomic conditions on the Wirral range between the deprived inner city and affluent suburbs, but with few from ethnic minorities. The study was introduced to the women by clinic midwives who asked for their agreement to be approached by study research midwives when they attended for ultrasound scanning at 20 weeks gestation. After complete description of the study to the women, written informed consent was obtained by the study midwives, who then administered questionnaires and an interview in the clinic.

Participants

Of those approached by study midwives, 68.4% gave consent and completed the measures, yielding an extensive sample of 1233 mothers with surviving singleton babies. The sampling flow chart has been published previously.22 The mean age at recruitment of extensive sample participants was 26.8 years (s.d. 5.8, range 18–51). Using the UK Index of Multiple Deprivation (IMD)23 based on data collected from the UK Census in 2001, 41.8% of the extensive sample reported socioeconomic profiles found in the most deprived UK quintile, consistent with the high levels of deprivation in some parts of the Wirral. Forty eight women (3.9%) described themselves as other than white British. Demographic and antenatal stratification measures were administered at 20 weeks gestation with all extensive sample participants.

A stratified random subsample of 316 mothers was recruited to the intensive sample at 32 weeks gestation with the sampling fraction depending on their prior responses to a measure of partner psychological abuse on entry into the extensive study at 20 weeks gestation.22 In addition to assessments of the mothers at 20 and 32 weeks gestation, mothers and infants generated data at 5, 9, and 29 weeks, and at 14 months. Two hundred and sixty eight mothers and infants came into the lab at 14 months for detailed observational, interview and physiological measures. Seven parents declined consent for DNA collection, 3 samples were spoilt, and 25 assessments were curtailed before saliva collection because of time constraints. Sufficient DNA for methylation analyses was obtained from 181 infants.

Measures

Maternal depression. Maternal symptoms of depression were assessed at 20 and 32 weeks’ gestation, and when infants were 5, 9 and 29 weeks, and 14 months, using the Edinburgh Postnatal Depression Scale (EPDS) which has been used extensively to assess pre- and postnatal depression.22 The measure was designed specifically to avoid confounding by symptoms commonly experienced by non-depressed women shortly after childbirth.

Maternal stroking. Maternal stroking was assessed by self report using the Parent-Infant Caregiving Scale (Sharp et al., 2012) in which mothers completed four items reporting on how often (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = a lot) they currently stroked their baby’s face, back, tummy, arms and legs. The four stroking items assess a stroking construct as evidenced in high loadings of all of the items on a latent variable24 and test-retest reliability over 4 weeks is acceptable (r = 0.58). Separate analyses were conducted with stroking at 5 and 9 weeks.

DNA methylation. Methylation status in the NR3C1 1-F promoter was examined at the same CpGs (CpG unit 22 and 23, see Figure 1) identified by Oberlander et al.,16 Conard et al.,19 Hompes et al.,17 Tyrka et al.20 and Melas et al.19 DNA collected from Oragene saliva samples was extracted, bisulphite treated, amplified (Forward, 5′-GACCTGGTCTCTCTGGGG-3′; Reverse, 5′-TGCACCCCGTACCCCCCTTT-3′) and run on a Sequenom EpiTYPER system (Sequenom, San Diego, CA, USA). Data were transformed to percentage of methylation at CpG unit 22 and 23 to allow for comparison with previous analysis of differential methylation at this locus.

Stratification variable and confounders. Partner psychological abuse was assessed using a 20-item questionnaire covering humiliating, demeaning or threatening utterances in the partner relationship during pregnancy over the previous year.22 Maternal stroking was assessed by self report using the Parent-Infant Caregiving Scale (Sharp et al., 2012) in which mothers completed four items reporting on how often (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = a lot) they currently stroked their baby’s face, back, tummy, arms and legs. The four stroking items assess a stroking construct as evidenced in high loadings of all of the items on a latent variable24 and test-retest reliability over 4 weeks is acceptable (r = 0.58). Separate analyses were conducted with stroking at 5 and 9 weeks.

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RESULTS

Maternal depression (EPDS) scores at 20 weeks’ gestation were strongly associated with mean EPDS across the four postnatal assessment points ($r = 0.68$). In separate ordinal logistic regression analyses, elevated methylation in the infants were predicted by EPDS scores at 20 weeks of pregnancy (log-odds coefficient $= 0.348$, s.e. $= 0.139$, $P = 0.013$) and mean postnatal EPDS scores (coefficient $= 0.574$, s.e. $= 0.141$, $P < 0.001$). When examined jointly, the interaction between 20 weeks’ prenatal and mean postnatal depression scores was significant (coefficient $= -0.418$, s.e. $= 0.207$, $P = 0.045$). The effect of the interaction on raw methylation percentage in the infants is illustrated in Figure 2, where groups below and above the median 20 weeks’ EPDS scores are contrasted. It can be seen that increasing postnatal depression was associated with increasing methylation only in infants from mothers below the median for prenatal depression.

We hypothesized that if maternal stroking reverses the effects of prenatal and postnatal depression on NR3C1 1-F promoter methylation, it should be associated with reduced methylation in the children of mothers with the combination of low prenatal and high postnatal depression. In view of the evidence that in rodents the effect of licking and grooming is limited to a short postnatal critical period, the effects of stroking at 5 and at 9 weeks were analyzed separately. Because low maternal prenatal depression is associated with low postnatal depression, the group that we identified below the median on prenatal depression and above the median on postnatal depression was relatively small ($N = 16$). These children had substantially higher methylation levels than their counterparts.

Figure 2. Child NR3C1 1-F promoter methylation percent by standardized maternal postnatal depression scores. The figure gives the locally weighted scatterplot smoothing (LOWESS) plots showing how the child’s raw methylation percent increases with increased maternal postnatal depression for those with low maternal prenatal depression (dashed line) but not those with high prenatal depression (solid). To improve visualization, the point marked ‘a’ has been displaced (from methylation 29%) in the scatterplot (but conservatively retained in the LOWESS).

Figure 3. Child NR3C1 1-F promoter methylation percent by standardized maternal stroking scores. The figure gives the locally weighted scatterplot smoothing plots showing how the child’s raw methylation percent decreases with maternal stroking for children with mothers who reported low prenatal but high postnatal depression scores (solid line). No such decrease is seen for the remainder of the children (dashed).

Statistical analysis

All analyses were undertaken in Stata 13 (StataCorp, 2012). The two-phase stratified sample design allows estimates to be reported for the general population from the stratified subsample by the use of inverse probability weights. Weights took account not only of the original stratification but also of the sample attrition that took place up to the assessment and methylation assay at age 14 months including mothers’ age and years of education, maternal smoking and depression score in pregnancy, and a score of the number of items left incomplete at the initial assessment. To avoid undue influence of some extreme observations of rates of methylation, the rates were grouped into seven categories of methylation level with approximately equal frequency (septiles) and association with other variables analyzed by means of weighted ordinal logistic regression. Reported effect estimates are thus log-odds coefficients. Stata’s svy option was used with standard errors and $P$-values based on the robust estimator of the parameter covariance matrix. Variation in the weights associated with the covariates of each model was removed to improve efficiency. Predictions of methylation levels were examined first including only variables of interest, and then after adding potential confounders for obstetric risk index, self-reported maternal smoking at 20 and 32 weeks of pregnancy, self-reported alcohol consumption at 20 weeks, birth weight by gestational age, neighborhood deprivation, maternal age, marital status and 20-week psychological abuse score.

Figures 2 and 3 show locally weighted scatterplot smoothing plots fitted to the raw methylation data. These are not based on model-predicted values but are empirical plots and are unweighted. The locally weighted scatterplot smoothing plots were fitted to the original raw data; whereas for the scatter plots, one marked observed methylation value was recorded from 29 to 14 to improve visualization.
the other 165 (coefficient = 1.688, s.e. = 0.510, P = 0.001). Increased
maternal stroking at 5 weeks specifically reduced methylation in this
group as evidenced in a highly significant statistical
interaction between the membership of this group and maternal
stroking when infants were 5 weeks old (coefficient = −2.754,
s.d. = 0.573, P < 0.001). This interaction was unaltered after the
addition of confounders to the model (coefficient = −2.634,
s.e. = 0.567, P < 0.001). The interaction is illustrated in Figure 3,
where it can be seen that with increasing maternal stroking,
NR3C1 1-F promoter methylation in the children of mothers in the
low prenatal and high postnatal group fell to the level of the
remainder of the sample. By contrast, there was no effect of
maternal stroking at 9 weeks of age (data not shown) highlighting
the importance of the early postnatal period.

DISCUSSION

We report two novel findings, first on the interactive effects of prenatal and postnatal maternal depression, and second on the
effect of maternal stroking, on NR3C1 1-F promoter methylation, in
young children. The interaction between prenatal and postnatal depression arose because the association between maternal
depression measured at four postnatal time points and NR3C1
1-F promoter methylation was stronger in infants who had been
exposed to low levels of maternal depression in utero. The effect
of maternal stroking was seen only in those infants exposed to
the combination of low prenatal and high postnatal maternal
depression.

Although the sample size of the study was modest, we reduced
the risks arising from multiple analyses by examining only one
CpG site, prespecified from other studies in the field. Previous
studies in humans had also identified maternal depression as a
predictor of NR3C1 1-F promoter methylation, which we measured
respectively both pre- and postnatally. The measure of maternal
stroking was by self-report, and it remains to be established
whether observed maternal stroking has the same effect. However,
observational measures are generally limited in the
studies of human development by restricted coverage over place
and time, and we have previously used this measure to show that
maternal stroking reverses the effects of prenatal depression on
physiological and behavioral reactivity at 29 weeks.32 We did not
test duplicate DNA samples, so any instability in methylation levels
may have contributed unmeasured error to the analyses. The
majority of the DNA extracted from whole saliva has been shown
to originate from blood leukocytes33,34 and previous studies on
NR3C1 methylation have generated similar results by utilizing the
DNA from brain7,9 and leukocytes10,14,16,18. These data further
support that adversities in early life may both be epigenetically
reflected in the central nervous system and in the peripheral
tissues (like leukocytes).

To the best of our knowledge, this is the first study in humans or
in animals to examine the interactive effects of pre- and postnatal
depression on DNA methylation. The findings reported in this
paper that the infants of mothers with low prenatal depression
were vulnerable to the effects of postnatal depression are
consistent with an interplay between prenatal and postnatal
environments seen throughout biology. From the effects of
exposure to chemical traces of a predator on the offspring of the
freshwater crustacean Daphnia, to the long-term effects of
restricted fetal growth in humans, prenatal exposure to a risk can
confer protection from the effects of postnatal experiences.35,36. In
general terms, this is consistent with the fetal origins hypothesis of
human disease that proposes that in utero environmental
exposures lead to modifications in fetal development, which are
adaptive where the subsequent postnatal environment is similar.
Discontinuities between prenatal and postnatal environments
create vulnerability. This effect is best exemplified in the
associations of low fetal growth with diabetes and hypertension
over several decades, that are thought to arise from fetal
adaptations that confer advantage in food-scarce environments
but create risk in western food-rich environments.35 Low birth
weight is also associated with adolescent depression in the
presence of childhood adversities, consistent with the
hypothesis.37 Possible mechanisms for the interplay between
prenatal and postnatal effects,3 and highlight the importance of translational research in linking the studies in animals to humans, with considerable
implications for our understanding of the earliest origins of
neurobiological and behavioral development, and psychiatric
disorders. Equally they imply new directions for animal models.
In addition to the studies of single pre- or postnatal stressors, the
effects of successive stressors need to be examined, in particular,
to test for modification by prenatal stress of effects of postnatal
stress, and to establish mechanisms. Similarly, not enough is
yet known about the ability of postnatal tactile stimulation to reverse
the effects of pre- and postnatal stressors, and about associated
epigeneic mechanisms. More broadly, human studies, informed
by animal models, have the potential to inform the design of
animal investigations to bring them closer to the human
condition.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease.
Nat Rev Neurosci 2005; 6: 463–475.
2. Weaver IC, Cervoni N, Champagne FA, D’Alessio AC, Sharma S, Seckl JR et al.
Epigenetic programming by maternal behavior. Nat Neurosci 2004; 7: 847–854.
3. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmühl Y, Fischer D et al. Dynamic
DNA methylation programs persistent adverse effects of early-life stress. Nat
Neurosci 2009; 12: 1559–1566.
4. Barker ED, Jaffee SR, Uher R, Maughan B. The contribution of prenatal and
postnatal maternal anxiety and depression to child maladjustment. Depress
Anxiety 2011; 28: 696–703.
5. O’Connor TG, Heron J, Golding J, Glover V, ALSPAC Study Team. Maternal
antenatal anxiety and behavioural/emotional problems in children: a test of a
programming hypothesis. J Child Psychol Psychiatry 2003; 44: 1025–1036.
6. Barker ED, Maughan B. Differentiating early-onset persistent versus childhood-
limited conduct problem youth. Am J Psychiatry 2009; 166: 900–908.
7. Davis EP, Glynn LM, Schetter CD, Hobel C, Chicz-Demet A, Sandman CA et al.
Prenatal exposure to maternal depression and cortisol influences infant tem-
perament. J Am Acad Child Adolesc Psychiatry 2007; 46: 737–746.
8. Davis EP, Glynn LM, Walfarm F, Sandman CA. Prenatal maternal stress programs
infant stress regulation. J Child Psychol Psychiatry 2011; 52: 119–129.
9. McGowan PO, Sasaki A, D’Alessio AC, Dymov S, Labonte B, Smyl M et al. Epigenetic
regulation of the glucocorticoid receptor in human brain associates with
cortisol sensitivity. Nat Neurosci 2008; 11: 97–106.
10. Oberlander TF, Weinberg J, Papdorf M, Grunau R, Misiu S, Devlin AM. Prenatal
exposure to maternal depression, neonatal methylation of human glucocorticoid
receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 2008;
3: 97–106.
11. Radtke KM, Ruf M, Gunter HM, Dohrmann K, Schauer M, Meyer A. Trans-
national Psychiatry (2015), 1–5
translational investigation of intimate partner violence on methylation in the promoter
of the glucocorticoid receptor. Transl Psychiatry 2011; 1: e21.
12. Mulligan CJ, D’Errico NC, Stees J, Hughes DA. Methylation changes at NR3C1 in
newborns associate with maternal prenatal stress exposure and newborn
birth weight. Epigenetics 2012; 7: 853–857.
13. Perroud N, Paoloni-Giacobino A, Prada P, Olje E, Salzmann A, Nicastro R et al.
Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a
history of childhood maltreatment: a link with the severity and type of trauma. Transl Psychiatry 2011; 1: e59.

14 Tyrka AR, Price LH, Maris C, Walters OC, Carpenter LL. Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: preliminary findings in healthy adults. PLoS One 2012; 7: e30148.

15 Perroud N, Dayer A, Piaget C, Nallet A, Favre S, Malafosse A et al. Childhood maltreatment and methylation of the glucocorticoid receptor gene NR3C1 in bipolar disorder. Br J Psychiatry 2013; 204: 30–35.

16 Conradt E, Lester BM, Appleton AA, Armstrong DA, Marsit CJ. The roles of DNA methylation of NR3C1 and 11β-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. Epigenetics 2013; 8: 1321–1329.

17 Hompes T, Izi B, Gellens E, Morreels M, Fieuws S, Peeters A et al. Investigating the influence of maternal cortisol and emotional state during pregnancy on the DNA methylation status of the glucocorticoid receptor gene (NR3C1) promoter region in cord blood. J Psychiatry Res 2013; 47: 880–891.

18 Melas PA, Wei Y, Wong CC, Sjoholm AK, Aberg E, Mill J et al. Genetic and epigenetic associations of MAOA and NR3C1 with depression and childhood adversities. Int J Neuropsychopharmacol 2013; 1: 1–16.

19 Meany MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. Dialogues Clin Neurosci 2005; 7: 103–123.

20 Lemaire V, Lamarque S, Le MM, Piazza PV, Abrous DN. Postnatal stimulation of the pups counteracts prenatal stress-induced deficits in hippocampal neurogenesis. Biol Psychiatry 2006; 59: 786–792.

21 Del Cerro MC, Perez-Laso C, Ortega E, Martin JL, Gomez F, Perez-Izquierdo MA et al. Maternal care counteracts behavioral effects of prenatal environmental stress in female rats. Behav Brain Res 2010; 208: 593–602.

22 Sharp H, Pickles A, Meaney M, Marshall K, Tibu F, Hill J. Frequency of infant stroking reported by mothers moderates the effect of prenatal environmental stress on infant behavioural and physiological outcomes. PLoS One 2012; 7: e45446.

23 Sharp H, Hill J, Hellier J, Pickles A. Maternal antenatal anxiety, postnatal stroking and emotional problems in children: outcomes predicted from pre- and postnatal programming hypotheses. Psychol Med 2014, 28: 1–15.

24 Noble MWright GDiben CSmith GMcLennan DAntilla CEt al. The English Indices of Deprivation 2004 (revised). Report to the Office of the Deputy Prime Minister. Neighbourhood Renewal Unit: London, UK, 2004.

25 Cox JL, Chapman G, Marsay D, Jones P. Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord 1996; 39: 185–189.

26 Moffitt TE, Caspi A, Mangolin G, Krueger RF, Magdol L, Silva PA et al. Do partners agree about abuse in their relationship? A psychometric evaluation of inter-partner agreement. Psychol Assess 1997; 9: 47–56.

27 Matheson FL, Moineddin R, Dunn JR, Creature MI, Goddy P, Glazier RH. Urban neighborhoods, chronic stress, gender and depression. Soc Sci Med 2006; 63: 2604–2616.

28 Knopik VS, Maccani MA, Franciazo S, McGee RE. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Dev Psychopathol 2012; 24: 1377–1390.

29 Lauffer BI, Mantha K, Kleiber ML, Diehl EJ, Addison SM, Singh SM. Long-lasting alterations to DNA methylation and ncRNAs could underlie the effects of fetal alcohol exposure in mice. Dis Model Mech 2013; 6: 977–992.

30 Hodes GE. Sex, stress, and epigenetics: regulation of behavior in animal models of mood disorders. Biol Sex Differ 2013; 4: 1.

31 Beck JE, Shaw DS. The influence of perinatal complications and environmental adversity on boys’ antisocial behavior. J Child Psychol Psychiatry 2005; 46: 35–46.

32 Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 1979; 74: 829–836.

33 Endler G, Greinix H, Winkler K, Mitterbauer G, Mannhalter C. Genetic fingerprinting in mouthwashes of patients after allogeneic bone marrow transplantation. Bone Marrow Transplant 1999; 24: 95–98.

34 Thiede C, Prange-Krex G, Freiberg-Richter J, Bornhauser M, Ehninger G. Buccal swabs but not mouthwash samples can be used to obtain pretransplant DNA fingerprints from recipients of allogeneic bone marrow transplants. Bone Marrow Transplant 2000; 25: 575–577.

35 Barker DJ. Fetal origins of coronary heart disease. BMJ 1995; 311: 171–174.

36 Bateson P, Barker D, Clutton-Brock T, Deb D, D’Udine B, Foley RA et al. Developmental plasticity and human health. Nature 2004; 430: 419–421.

37 Costello EJ, Worthman C, Erkanli A, Angold A. Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. Arch Gen Psychiatry 2007; 64: 338–344.

38 MacKenzie A, Quinn J. A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. Proc Natl Acad Sci USA 1999; 96: 15251–15255.