

# Prenatal risk factors for depression: a critical review of the evidence and potential mechanisms

E. C. Braithwaite<sup>1\*</sup>, S. E. Murphy<sup>1</sup> and P. G. Ramchandani<sup>2</sup>

<sup>1</sup>Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

<sup>2</sup>Academic Unit of Child & Adolescent Psychiatry, Imperial College, St Mary's Campus, London, UK

Exposure to adverse experiences in early life increases the risk of depression during adulthood. Recent findings have highlighted that exposure of a fetus to an adverse intrauterine environment may also have implications for later offspring depression. This review considers the status of the evidence for these associations and the potential mechanisms underlying prenatal developmental risks for later depression, addressing the challenging possibility that environmental predisposition to depression may begin before birth.

Received 21 November 2013; Revised 28 May 2014; Accepted 29 May 2014; First published online 20 June 2014

**Key words:** depression, fetal programming, prenatal adversity

## Introduction

Depression is characterized by persistent low mood and associated cognitive, emotional and physical symptoms, such as low self-esteem, and disturbed sleep and appetite. Depression is the 4th leading cause of disability worldwide; each year 6% of adults experience an episode of depression, and over the course of a lifetime, 15–20% of the population will have at least one depressive episode.<sup>1</sup> At a biological level, depression involves changes in monoamine neurotransmitters, hypothalamic–pituitary–adrenal (HPA) axis function, and immune system alterations; however the exact pathophysiology and etiology remains unclear.

A number of risk factors are associated with depression onset. These include: genetic<sup>2</sup> and personality risk factors;<sup>3</sup> psychosocial factors such as unemployment and poverty;<sup>4</sup> and comorbidities with other diseases such as diabetes and cardiovascular disease.<sup>5</sup> Over the past decade it has become increasingly clear that environmental stressors during early life, such as childhood maltreatment, also increase risk of depression. Consistent findings from humans and animals support an association between early life stress and childhood and adult psychopathology, particularly depressive symptoms.<sup>6–11</sup>

A relevant new concept in this field, which has come to the forefront of the literature recently, is that risk factors for depression may present even earlier than previously thought: risk for depression may extend into the *prenatal* period. That is, a fetus that is exposed to a compromised intrauterine environment may be predisposed to develop depression in adulthood. For example, there have been consistent findings of associations between high levels of maternal prenatal stress, and adverse

offspring outcomes,<sup>12–14</sup> including depression.<sup>15</sup> This raises the intriguing possibility that risk for depression may, in some cases, be determined before birth.

However, given this notion is in its infancy, there is currently little information about the nature of prenatal environmental adversity, timing of exposure, and mechanism by which prenatal environmental factors may increase risk for offspring depression. This review is a focused overview of the current state of the literature that provides evidence for associations between prenatal environmental exposures and offspring depression. We begin with a discussion of the role of low birth weight (LBW) in the prediction of adult health and disease, in line with the Barker hypothesis, before considering a number of key fetal exposures for depression in adulthood, including: maternal undernutrition, psychological distress and toxin exposure. We then discuss potential mechanisms by which the intrauterine environment may influence offspring depression risk, and the challenges of unravelling such mechanisms.

## Developmental origins of health hypothesis

The recent impetus to study antenatal factors as markers of later health risk originated with a consideration of LBW. In 1989, Barker reported an association between LBW and cardiovascular disease and diabetes, such that infants born with LBW were more likely to develop cardiovascular disease and diabetes in adulthood.<sup>16,17</sup> Although the underlying cause of the LBW was unclear, it was evident that the infant's growth within the womb had been compromised. This research highlighted the possibility that environmental factors within the womb may have implications for adult health and disease; until this time it was widely assumed that the intrauterine environment was protected from outside influences. From this research the 'Barker hypothesis', or 'fetal programming hypothesis', was

\*Address for correspondence: E. Braithwaite, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK.  
(Email Elizabeth.braithwaite@psych.ox.ac.uk)

formed, which proposes that the developing fetus adapts to maternal cues within the womb, and that this adaptation has the aim of ultimately increasing the chance of offspring survival. Recently, the fetal programming hypothesis has been expanded to explain in evolutionary terms how other environmental factors, such as maternal prenatal stress, may result in adverse offspring outcomes.<sup>14,18</sup> It has been suggested that high levels of maternal stress during pregnancy may be as a result of environmental pressures such as competition for food or conflict with rival groups. As such, the fetus responds to maternal cues that the postnatal environment will be one of adversity, and adapts in a way that would be beneficial for survival in such a stressful environment. For example, the child may be more likely to be aggressive and have a rapidly distracted attention,<sup>14,18</sup> which could benefit survival in such a high-stress environment.

Here, we consider the evidence from human studies in relation to the outcome of depression in adult life; in particular those studies assessing the hypothesis that LBW, maternal undernutrition, psychological distress and toxin exposure during pregnancy may predispose offspring to increased risk for depression.

### Low birth weight and offspring depression

LBW is a crude indicator of intrauterine growth restriction, and is commonly associated with undernutrition in pregnancy. However, there are a number of problems with using LBW as a proxy for prenatal adversity, as the exact cause of the LBW cannot be determined. For example, LBW is not only associated with maternal undernutrition, but is also related to smoking<sup>19–21</sup> and psychosocial stress<sup>22–24</sup> during pregnancy. Further, LBW is often not dissociated from small for gestational age (SGA), and it is likely that the two have different origins. Nonetheless, numerous early studies of development used LBW as a measure of sub-optimal intrauterine growth, and the results still offer useful insights into the effects of the fetal environment on later health outcomes.

Since the initial findings from Barker, a still-growing body of research has linked LBW to a variety of adult health outcomes, including: cardiovascular disease,<sup>16,25,26</sup> hypertension,<sup>27</sup> and type 2 diabetes.<sup>28</sup> The literature regarding the association between low LBW and adult depression however is conflicting, with evidence both for<sup>29–35</sup> and against<sup>36–39</sup> an association. A recent meta-analysis of 18 studies found a weak association between LBW and later depression/psychological stress (OR = 1.15, 95% CI = 1–1.32).<sup>40</sup> However, this association attenuated after correcting for potential publication bias (OR = 1.08, 95% CI = 0.92–1.27), and also when the analysis was restricted to examining depression alone. Therefore, there is currently insufficient evidence to support the hypothesis that LBW is associated with later depression. Just one study has considered SGA, independently of LBW, as a risk for adult depression. Haavind *et al.*<sup>41</sup> assessed 8519 adolescents, and similarly found that those who were SGA were no more likely to have depression or anxiety than controls. Considering that inconsistencies in the LBW literature

could potentially be due to individual variation in underlying causes of LBW, it is possible that more accurate and concise measures of intrauterine growth restriction may yield more reliable findings.

### Maternal undernutrition during pregnancy and offspring depression

The 1944 Dutch famine provided a unique opportunity to directly examine the impact of maternal undernutrition. This famine took place as a result of a transport embargo on food supplies imposed by the German occupying forces in the Netherlands during WWII. Official rations fell below 900 kcal/day by November 1944, and were as low as 500 kcal/day by April 1945. The dramatic effects of the famine on the course and outcome of pregnancy have been recorded,<sup>42,43</sup> and follow-up studies have documented long-term consequences among the offspring.<sup>44–47</sup> In 2000, Brown *et al.* identified that risk of developing an affective disorder was significantly increased for those exposed to famine during the second and third trimesters, compared to an unexposed control group (OR = 1.5,  $P < 0.05$ ). These effects were present in both men and women, and for unipolar and bipolar affective disorders.<sup>48</sup> Further findings from this cohort have reported increases specifically in depressive symptoms of prenatally exposed adults, compared with sibling and hospital controls (OR = 1.27,  $P < 0.05$ ).<sup>49</sup> However, it is important to consider that these adults were also exposed to high levels of prenatal stress, and it has been suggested that prenatal malnutrition and stress may exert effects on fetal neurodevelopment via similar mechanisms.<sup>50</sup>

It is also important to consider that famine during wartime is extreme, and perhaps not reflective of the undernutrition that many women around the world may experience during pregnancy today, which may be indexed by low body mass index or by a current eating disorder. Findings from the Avon longitudinal Study of Parents and Children (ALSPAC) cohort have linked eating disorders during pregnancy with an increased rate of emotional, conduct and hyperactivity disorders in childhood<sup>51</sup> and with adolescent emotional disorders.<sup>52</sup> However, there is a distinct lack of data linking prenatal low BMI or eating disorders with offspring depression and the findings from the Dutch famine cohort require replication.

### Maternal psychological distress during pregnancy and offspring depression

Many studies have shown that prenatal maternal psychological stress increases risk of child emotional and behavioral problems.<sup>12,14,53,54</sup> However, to date relatively few have followed offspring into adulthood, which is when the incidence of depression increases significantly. Three studies have reported offspring depression in the context of prenatal stress (see Table 1). A prospective observational study of 120 mother-offspring dyads found that adolescents aged 11–16 years were 4.4 times more likely to have a diagnosis of depressive disorder

**Table 1.** Summary of studies which have investigated specific prenatal environmental exposures and offspring depressive symptoms

	Fetal exposure	N	Measure of adverse fetal environment	Measure of offspring depression	Age of offspring at assessment	Main result of study
Brown <i>et al.</i> (2000)	Maternal undernutrition	40,000 +	Maternal exposure to the Dutch Hunger Winter during the second and third trimester	Cases of major affective disorder requiring hospitalization were newly ascertained from a national psychiatric registry	>18 years	Risk of developing major affective disorder was increased for subjects with exposure to famine during the second and third trimester ( $\chi^2 = 5.07, P < 0.05$ )
Stein <i>et al.</i> (2009)		923	Maternal exposure to the Dutch Hunger Winter during the second and third trimester	Center for Epidemiologic Studies Depression Scale	59 years	Prenatal exposure to famine was associated with a 0.96-point increased depression score ( $P < 0.05$ )
Van den Bergh <i>et al.</i> (2008)	Maternal psychological distress	58	Maternal antenatal anxiety assessed during the first, second and third weeks of pregnancy with the STAI	CDI	14–15 years	Exposure to first trimester anxiety in both sexes was associated with a high, flattened cortisol day-time profile ( $t_{56} = -2.03, P < 0.05$ ) and in females only this predicted depressive symptoms ( $\omega^2 = 0.14, P < 0.01$ )
Pawlby <i>et al.</i> (2011)		120	Maternal antenatal depression was measured at 36 weeks gestation using the CIS	DSM-IV diagnoses were generated from the combined reports of parent and child using the child and adolescent psychiatric assessment	11–16 years	Offspring who had been exposed both to maternal depression <i>in utero</i> and to childhood maltreatment were 3.2 times more likely than those exposed to neither, to have a diagnosis of a depressive disorder at 11 and/or 16 years. In contrast, children who were exposed only to maternal antenatal depression or to childhood maltreatment were no more at risk of having depression
Pearson <i>et al.</i> (2013)		8,937	Maternal antenatal depression was measured at 18 and 32 weeks of pregnancy using the EPDS	Diagnosis of major depression using ICD-10	18 years	Offspring were 1.28 times more likely to have depression at 18 for each s.d. increase in maternal antenatal depression (95% CI = 1.08–1.51, $P = 0.003$ ), which was independent of maternal postnatal depression
Barr <i>et al.</i> (2006)	Alcohol	431	Maternal alcohol consumption during pregnancy assessed by self-report during early and mid-pregnancy	Structured clinical interview for DSM-IV	Average 25.7 years	Prenatal alcohol exposure resulted in a 1.60 odds ratio increase in depressive symptoms at age 25 (95% CI = 0.95–2.68)
Famy <i>et al.</i> (1998)		25	25 subjects who met criteria for fetal alcohol syndrome were selected from a large, ongoing study of fetal alcohol syndrome	Structured clinical interview for DSM-IV	above 18 years	Of the 25 participants, 10 were diagnosed with depression

Table 1. (Continued)

	Fetal exposure	N	Measure of adverse fetal environment	Measure of offspring depression	Age of offspring at assessment	Main result of study
O'Connor and Kasari (2000)		41	Retrospective maternal report of alcohol consumption during pregnancy, when the infant was 1 year old	PDS	5–6 years	Prenatal alcohol exposure was associated with infant depressive symptoms ( $R^2 = 0.32$ , $P < 0.05$ )
O'Connor and Paley (2005)		42	Retrospective maternal report of prenatal alcohol consumption. Measure used was maximum drinks per occasion	PDS	4–5 years	Child negative affect was related to prenatal alcohol use ( $R = 0.47$ , $P < 0.001$ )
Fergusson <i>et al.</i> (1998)	Smoking	1265	Maternal self-report of smoking during pregnancy	Structured clinical interview for DSM-IV	18 years	Those exposed to maternal smoking during pregnancy had higher rates of major depression [ $F_{(1,1020)} = 4.71$ , $P < 0.05$ ]
Liu <i>et al.</i> (2011)		611	Maternal self-report of smoking during pregnancy	Center for Epidemiologic Studies Depression Scale (short version)	Repeated measures at 1, 4 and 7 years	No association was found between maternal prenatal smoking and offspring depressive symptoms
Cornelius <i>et al.</i> (2012)		608	Maternal self-report of smoking during pregnancy	The ASR questionnaire	22 years	There was a significant bivariate association between prenatal cigarette smoke exposure and offspring depression/anxiety
Menezes <i>et al.</i> (2013)		5249	Maternal self-report of smoking during pregnancy	Mini International Psychiatric Interview	18 years	The prevalence of offspring depression increased as smoking in pregnancy increased [ $<20$ cigarettes/day OR = 1.38 (95% CI = 1.03–1.84) and $>20$ cigarettes/day OR = 2.11 (95% CI = 1.31–3.40)]
Gray <i>et al.</i> (2005)	Cannabis	633	Maternal self-report of marijuana use during pregnancy	CDI	10 years	Child depressive symptoms were predicted by maternal marijuana use in the first and third trimesters ( $\beta = 1.83$ , $P < 0.01$ )
Goldschmidt <i>et al.</i> (2004)		606	Maternal self-report of marijuana use during pregnancy	CDI	11 years	First trimester cannabis consumption was significantly associated with child self-reported depressive symptoms ( $P < 0.01$ )
Leech <i>et al.</i> (2006)		636	Maternal self-report of marijuana use during pregnancy	CDI	10 years	Prenatal exposure to cannabis predicted child depressive and anxiety symptoms at age 10 ( $P < 0.05$ )

STAI, state trait anxiety inventory; CDI, children's depression symptoms inventory; CIS, clinical interview schedule; EPDS, Edinburgh Postnatal Depression Scale; PDS, Pictorial Depression Scale; ASR, adult self-report.

when exposed to antenatal depression and childhood maltreatment.<sup>55</sup> However, those offspring exposed only to antenatal depression or childhood maltreatment were no more at risk of having depression. Van den Bergh *et al.* investigated the effects of prenatal mood disturbance on adolescent depression ( $n = 58$ ). They found that 14 and 15-year-old adolescents exposed to prenatal anxiety had a high, flattened cortisol daytime profile ( $P < 0.05$ ) and in females only, this was associated with increased depressive symptoms ( $P < 0.01$ ).<sup>15</sup> Similarly, in a larger study of over 4500 mother–infant dyads using data from the ALSPAC cohort, Pearson *et al.* also found that offspring were 1.28 times more likely to have depression at 18 years of age for each standard deviation increase in maternal antenatal depression (95% CI = 1.08–1.51,  $P < 0.01$ ),<sup>56</sup> and this remained significant when controlling for confounding variables. Thus, although there is some discrepancy, two of these three initial studies are suggestive of a significant and positive association between maternal psychological distress during pregnancy and offspring depression.

### Maternal exposure to environmental toxins during pregnancy

#### Alcohol

Fetal alcohol spectrum disorder (FASD) is an over-arching term used to describe the range of adverse effects that can occur in children of women who consume alcohol during pregnancy. Fetal alcohol syndrome is the most severe end of the spectrum, and can occur as a result of chronic consumption of alcohol during pregnancy.<sup>57</sup> FASD presents a number of central nervous system defects, including: diminished intellectual capacity, deficits in executive function, and a wide range of maladaptive and clinically significant behavioral characteristics.<sup>58</sup> A number of studies have also found an association between FASD and depressive symptoms during both childhood and adulthood.<sup>59–62</sup> However, these studies have a number of limitations, which should be considered. Famy *et al.* reported that adults with FASD suffer from mental illness, including depression, but this descriptive study is limited by a small sample ( $n = 25$ ) with no control group. Two studies by O'Connor *et al.* reported an association between maternal alcohol consumption during pregnancy and child depressive symptoms at age 4–6 years. However, these two studies again had very small sample sizes ( $n = 41$  and  $42$ ), and the statistical analysis of these studies was limited, for example no multivariate analyses were used. Just one larger cohort study with 400 mother–infant dyads has investigated this association; Barr *et al.* found no significant increase in depression risk following prenatal alcohol exposure. Therefore, there is currently insufficient evidence to support a causal relationship between prenatal alcohol exposure and offspring depression.

#### Smoking

There is more convincing evidence from the human literature to suggest that maternal smoking during pregnancy influences

depressive symptoms. In a study of 611 children at age 7, those prenatally exposed to smoking had higher anger temperament scores than non-exposed controls, but no association was found between prenatal smoking exposure and other negative emotions, including depression and anxiety.<sup>63</sup> However, this may be attributable to the young age of the children, and an inability to detect significant levels of psychopathology. Two large birth cohort studies and a large observational study have assessed older adolescents and adults, and have all reported findings of a positive association. Cornelius *et al.* found a significant association between prenatal nicotine exposure and self-reported depression/anxiety at age 22 years ( $n = 608$ ).<sup>64</sup> Similarly, in a sample of 1265 participants at age 18, Fergusson *et al.*<sup>65</sup> reported that those exposed to prenatal nicotine had a higher incidence of major depressive disorder ( $P < 0.05$ ). Further, Menezes *et al.* analyzed data from a Brazilian cohort ( $n = 5249$ , aged 18), and found that prevalence of offspring depression increased as smoking in pregnancy increased [ $<20$  cigarettes/day OR = 1.38 (95% CI = 1.03–1.84) and  $>20$  cigarettes/day OR = 2.11 (95% CI = 1.31–3.40)].<sup>66</sup> Thus, initial findings suggest a positive and significant association between prenatal nicotine exposure and depression in late adolescence/early adulthood.

#### Cannabis

Research into the consequences of prenatal cannabis exposure has focused primarily on infant cognitive and behavioral development, and evidence regarding mental health outcomes is limited. However, one longitudinal study has documented this at the age of 10 years (see Table 1). A regression analysis found that prenatal cannabis use significantly predicted child depressive symptoms ( $\beta = 1.83$ ,  $P < 0.01$ ).<sup>67–69</sup> Interestingly, Grey *et al.* expanded their analysis to assess the effect of trimester, and found that while first trimester cannabis exposure predicted offspring depressive symptoms at 10 years, effects in the second and third trimester appeared to be accounted for by first trimester exposure. Therefore, it is possible that the first trimester may be a ‘sensitive period’ for prenatal cannabis exposure to influence offspring depressive symptoms.

### Fetal risk exposure and offspring depression: a summary

Few human studies have investigated the relationship between prenatal exposures and offspring depression, a summary is available in Table 1. These preliminary findings suggest that prenatal exposure to undernutrition, psychological distress and cannabis increase risk for offspring depression. However, it is important to note that the majority of measures of fetal exposures are based on retrospective maternal reports, which may be both unreliable due to reduced recall accuracy, and are also subject to reporter bias. It is also important to note that observational studies, such as those presented above, have a number of methodological limitations. For example, they are subject to residual confounding, which is the distortion that



remains after controlling for cofounders in the study design, and some also use repeated measures, which results in auto-correlation of variables. The ideal design to understand whether these risk factors are causal, and to model the mechanisms through which they may affect risk for depression, would be to use randomized intervention trials. Clearly for most of these risk exposures, such as drug use or undernutrition, it is not possible to do this ethically, so we have to rely on human evidence from the best alternative study designs, such as longitudinal studies and natural experiments. However, our knowledge is also supplemented by studies in animals, where a wider range of study designs can be undertaken.

Many of the risk factors addressed in this review have been modeled in animals, and in the main, the findings have been congruent. For example, prenatal exposure to acute stress, alcohol and cannabis has been associated with offspring depression and anxiety-like behaviors.<sup>19,70–73</sup> However, modeling prenatal risk factors in animals presents a number of challenges. Particularly, the methods used to induce stress, such as open field or elevated maze paradigms, have limited translational relevance to human antenatal mood disorder.

Outstanding questions remain regarding fetal risk exposure. For example, findings from Gray *et al.* suggest that the first trimester is a sensitive period for exposure to cannabis and the development of depressive symptoms. It is currently unclear, however, whether other fetal exposures also have a sensitive period of impact, and if so when that may be. It is also unclear whether the strength of exposure may impose its effect in a ‘dose-dependent’ manner. For example, it may be that chronic exposure to an adverse fetal exposure results in more severe offspring depressive symptoms than an acute exposure. It is not possible to currently address these questions directly in the human literature, as experimental study designs where the timing and intensity of prenatal risk are controlled are clearly unethical and unfeasible.

### Pathways of risk transmission from the prenatal environment to offspring depression

There are a number of real challenges to understanding the pathways of risk from the prenatal environment to offspring depression. First, it is extremely difficult to disentangle the individual effects of shared genes between mother and infant. Second, the continuation of some prenatal environmental exposures into the postnatal period makes separation of pre and post-natal exposures difficult. Finally, research disaggregating the remaining biological mechanisms occurring *in utero* that mediate these effects is in its infancy.

In this section, we briefly consider the roles of genetic and ongoing postnatal environmental exposure. However, there is evidence that there is an effect of prenatal environmental risk exposure over and above the effect of shared genes and post-natal environment. Therefore, the main focus of this section is on potential intrauterine biological mechanisms that might mediate prenatal risk exposure. The majority of the research

here has focused on programming of the fetal HPA axis; however we also consider the roles of the maternal immune and sympathetic nervous systems. It is also important to note that, in the main, this field of research has been conducted in the context of exposure to prenatal psychological distress.

### Shared genetics

Depression has a genetic component;<sup>74</sup> from twin studies it is estimated that heritability of Major Depressive Disorder is 0.33 (95% CI = 0.26–0.39).<sup>75</sup> A number of genotypes have been reported to increase risk or susceptibility to depression, such as the serotonin transporter polymorphism (5-HTTLPR)<sup>76</sup> and a single nucleotide polymorphism in the brain-derived neurotrophic factor gene.<sup>77</sup> However, a number of replication attempts have failed to identify susceptibility genes convincingly. A more recent approach to identifying genetic variants associated with depression is via genome-wide association studies,<sup>78–81</sup> however it has been estimated that a very large sample size upwards of 50,000 cases would be required to detect specific genes for depression.<sup>78</sup>

Nonetheless, as depression has a genetic component it is logical to presume that shared risk genes between the mother and offspring may underlie the relationship between prenatal environmental exposure and offspring depression. Consequently, teasing apart the independent influences of genetic and environmental factors poses a significant challenge.

In a very elegant study, Rice *et al.* capitalized on the use of *in vitro* fertilization, to design a ‘prenatal cross-fostering’ study in which pregnant mothers were genetically related or unrelated to their child, in order to disentangle maternally inherited and environmental influences on offspring.<sup>82</sup> They examined 574 mother-related dyads and 205 mother-unrelated dyads, and found that associations between prenatal stress and offspring birth weight, gestational age and antisocial behavior were evident in both the mother-related ( $\beta = 0.207$ ,  $P < 0.001$ ) and mother-unrelated pairs ( $\beta = 0.211$ ,  $P < 0.01$ ), which is consistent with the idea that prenatal stress is an important environmental influence. However, different patterns emerged for associations between prenatal stress and other outcomes such as anxiety. Although this study did not examine offspring depression specifically, it does offer useful insights into the independent roles of genes and environment in moderating the effects of prenatal stress on offspring outcomes. This study highlights that, although shared genes are important in this relationship, there is more to the association than genetics alone can account for, and therefore the environment must play a significant role.

### Continuation of environmental exposure

A further challenge is to dissociate the independent effects of the prenatal and postnatal environment. Often, adverse environmental influences are present during both the prenatal and postnatal period. For example, prenatal depression is the main risk factor for postnatal depression,<sup>83</sup> and women who

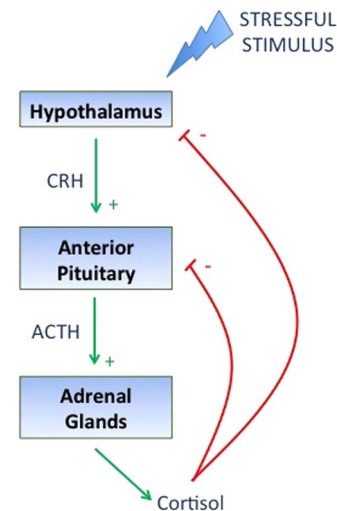
smoke while pregnant are also likely to smoke postnatally. Further, there is also evidence from the animal literature to suggest that prenatal stress has implications for postnatal maternal behavior, which potentially increases risk for offspring depression.<sup>84</sup> Thus, it is difficult to discern whether it is the prenatal or postnatal exposure, or both, which poses risk to offspring development. Another challenge is to understand whether prenatal and postnatal exposure may exert different influences on offspring development. To some extent this was addressed by Rice *et al.*, who found that maternal postnatal stress increased risk for offspring anxiety, whereas prenatal stress presented risk for antisocial behavior.<sup>82</sup> One approach, which has been used to infer causality from prenatal risk factors, is Mendelian randomization; genetic variants known to be reliably associated with a modifiable exposure are used to make inferences about those exposures and disease risk.<sup>85</sup> An alternative approach is via the use of large cohort studies, where it is possible to statistically partial out the effects of the postnatal environment in order to study independent prenatal effects. O'Connor *et al.* used this method in 2002. They found that maternal prenatal anxiety predicted infant emotional and behavioral problems in boys (OR = 2.14, 95% CI = 1.48–3.10) and girls (OR = 1.88, 95% CI = 1.30–2.69), which remained significant after controlling for postnatal anxiety.<sup>12</sup> Pearson *et al.* took the same approach when analyzing data from the ALSPAC cohort, as discussed previously. They found that antenatal depression was a significant risk factor for offspring depression, independently of postnatal depression.<sup>56</sup> Thus, the evidence points to an independent effect of the prenatal environment on offspring depression.

### Intrauterine biological mechanisms

It is clear that prenatal maternal psychological distress may increase risk for offspring depression, independently of the postnatal environment and shared genetics. This indicates that biological mechanisms *in utero* mediate at least part of the association between prenatal distress and offspring depression. A number of potential mechanisms have been proposed to explain this association, including: increased maternal noradrenaline, which may cause vasoconstriction and reduce fetal blood flow, and immunological mechanisms, which increase maternal inflammation. Of course, it is likely that a combination of mechanisms play a role in this association; however there is a paucity of research here. The majority of the research to date has focused on the programming of maternal and infant HPA axis as the biological mechanism linking prenatal stress with adverse offspring outcomes, arguably because it is the most accessible system to measure.

### HPA axis

The HPA axis forms a major part of the neuroendocrine system and has many biological roles, including regulation of stress responses. Acute stress initiates the release of corticotrophin-releasing hormone (CRH) from the hypothalamus, which



**Fig. 1.** Action of the HPA axis in response to a stressful stimulus. CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotropic hormone.

stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). This in turn initiates the release of glucocorticoid hormones (mainly cortisol) from the adrenal glands, which act to suppress the release of CRH and ACTH from the hypothalamus and anterior pituitary, via the activation of glucocorticoid receptors (GRs) in a negative feedback loop (see Fig. 1). Cortisol is the main stress hormone and has a number of biological effects in the body.

The HPA axis has been implicated in the etiology of depression: currently depressed individuals have over-active cortisol reactivity,<sup>86,87</sup> as do individuals with high genetic risk for depression,<sup>88,89</sup> and also those recovered from depression.<sup>90</sup> However, the evidence for dysregulation of the HPA axis as a marker of depression risk has not been entirely consistent.<sup>91–94</sup> The effects appear to be small and may be restricted to more severe symptoms of depression, and it unclear whether this relationship is causal.

Van den Burgh *et al.* were the first to demonstrate the involvement of the HPA axis in the link between prenatal mood disturbance and offspring depression in humans. 14–15-year-old adolescents exposed to prenatal anxiety had a high, flattened cortisol daytime profile and, in females only, this was associated with increased depressive symptoms.<sup>15</sup> In support, there is further evidence that increased maternal glucocorticoids during pregnancy alter infant HPA function. Davis *et al.*<sup>95</sup> found that elevated glucocorticoids during the second and third trimester predicted larger infant cortisol responses to the heel-stick procedure 24 h after birth. Similarly, Brennan *et al.*<sup>96</sup> showed that prenatal anxiety and depression predicted baseline and mean cortisol levels at 6 months, and O'Connor *et al.* found that prenatal anxiety was associated with individual differences in awakening and afternoon cortisol levels in 10-year-old children.<sup>97</sup> The animal literature also provides evidence that prenatal stress is associated with altered offspring

HPA function. Rodents exposed to prenatal restraint stress demonstrated enhanced activity of the HPA system,<sup>71</sup> corticosterone release was prolonged following stress exposure, and central GR expression was reduced.<sup>98</sup>

Some preliminary findings suggest that the process by which prenatal stress may influence offspring HPA function is via epigenetic changes. Epigenetics describes changes in gene activity that is not caused by a change in the DNA sequence. Examples of epigenetic changes are DNA methylation and histone modification. These mechanisms can alter gene expression, and are processes by which the environment can influence phenotype.

As mentioned above, prenatal restraint stress is associated with reduced GR expression, and evidence suggests that downregulation of the GR is mediated by epigenetic regulation of the GR gene, NR3C1. Chronic stress has been shown to increase methylation of NR3C1, which subsequently downregulates the receptors' expression. This results in an over-active stress response, as usually activation of the GR receptor initiates the negative feedback loop of the HPA axis, and 'turns off' cortisol release.<sup>99</sup> Exposure to early postnatal stress also results in increased methylation of the NR3C1 gene and subsequent downregulation of its expression in the hippocampus of both rodents<sup>100,101</sup> and humans.<sup>102</sup> Interestingly, Oberlander *et al.* found that newborns exposed prenatal depression also had increased methylation of the promoter region of the NR3C1 gene, and at 3 months this was associated with increased salivary cortisol response to an acute stressor.<sup>103</sup> Thus, the results of these initial studies suggest that exposure to maternal prenatal psychological distress causes increased methylation of the offspring NR3C1 gene, resulting in decreased hippocampal GR expression and reduced feed-back efficiency of the HPA system, leading to over-active and sustained stress responses.

The biological process linking raised maternal glucocorticoids with epigenetic alterations remain unclear, however recent research has begun to delineate this. Usually, maternal cortisol is metabolized at the placental barrier by the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase-2 (11 $\beta$ -HSD-2). However, when maternal cortisol levels are high, such as in the case of prenatal psychological distress, 11 $\beta$ -HSD-2 is downregulated, and more active cortisol enters fetal circulation.<sup>104–106</sup> Animal studies suggest that downregulation of 11 $\beta$ -HSD-2 is mediated by increased methylation of the 11 $\beta$ -HSD-2 gene promoter.<sup>107</sup> Thus, it appears that prenatal psychological distress is associated with offspring epigenetic alterations, which affect gene and protein expression in both the offspring brain and placenta. However, intracellular mechanisms linking fetal cortisol with epigenetic modifications remain unclear.

#### *Sympathetic nervous system*

Although this review has focused on the HPA axis mediating the link between prenatal psychological distress and offspring depression, it is likely that other mechanisms are also involved. Indeed, there appear to be rapid mechanisms which link maternal emotional state with fetal heart rate responses,<sup>108</sup>

which cannot be explained by the relatively slow activation of the HPA axis.

As well as the HPA axis, psychological distress also activates the sympathetic nervous system, which results in the release of noradrenaline. Noradrenaline does not directly cross the placenta;<sup>109</sup> however it is possible that its release could indirectly affect the fetus by initiating vasoconstriction and disrupting uterine blood flow. Human research in this field is limited, but a significant association between high anxiety during the third trimester and increased uterine artery resistance index has been demonstrated.<sup>110</sup> Further, animal research has shown that both acute stress exposure and intravenous infusions of noradrenaline induce decreased uterine blood flow.<sup>111,112</sup> Thus, sympathetic nervous system alterations could in part mediate the association between prenatal psychological distress and offspring depression.

#### *Immune system*

Antenatal stress has also been linked to offspring immune function in a number of animal studies.<sup>113–118</sup> Although these investigations have used a wide range of prenatal stress exposures and measures of offspring immune function, there is a consensus that prenatal stress is linked with compromised offspring immunity. Human studies have generally used indirect measures of infant immune function. For example, associations have been found between prenatal mood disturbance and infant asthma<sup>119,120</sup> and infectious disease.<sup>121</sup> Further, an association has been found between the method of delivery, as an index of maternal stress, and lymphocyte subset cell counts,<sup>122</sup> and prenatal stress has also been linked to altered innate and adaptive immune responses in cord blood mononuclear cells.<sup>123</sup>

One study has directly examined prenatal anxiety and adaptive immune responses of infants at 2 and 6 months of age to a hepatitis B vaccine. O'Connor *et al.*<sup>124</sup> reported that prenatal anxiety predicted lower hepatitis B titers at 6 months of age, and altered responder cell frequencies to antigen application. Thus suggesting that prenatal anxiety changes the adaptive immunity of the infant. Further, it highlights the possibility that immune system alterations may be one mechanism by which prenatal psychological distress exerts influence on offspring development.

#### *Pathways to transmission of risk: summary*

It is difficult to dissociate the pathways that mediate the relationship between prenatal environmental exposures and offspring depression, and it is likely that both shared genetic factors between mother and infant and continuation of exposure from the pre- to postnatal period contribute. Nonetheless, it is also clear that intrauterine biological mechanisms account, at least in part, for this association. The majority of the research has focused on alterations of the infant HPA axis. However, it is likely that a number of systems are affected in a complex manner as a result of a compromised intrauterine environment.



### Conclusions and future directions

In conclusion, a developing body of evidence suggests that depression may, in some cases, have a very early developmental origin. Although research to date is limited, it is suggestive of an association between fetal undernutrition, maternal psychological distress, cannabis exposure, and an increased risk of offspring depression. However, a number of key questions regarding this association remain unanswered. For example, it is currently unclear whether the intensity and timing of the exposure are significant outcome severity. Further, the full extent of biological mechanisms which may mediate this association are yet to be elucidated. More thorough and extensive longitudinal cohort studies, and intervention studies tackling depression and anxiety, are required to further characterize these associations, as well as detailed neurodevelopmental studies to fully understand the underlying mechanisms. Understanding these mechanisms is an extremely important step in targeting public health prenatal and postnatal interventions to best help 'at risk' mothers, and to potentially limit depression risk before birth.

### Acknowledgements

None.

### Financial Support

This research was funded by a UK Medical Research Council Studentship awarded to Miss Elizabeth Braithwaite (grant number MR/J500501/1). Dr Susannah E. Murphy is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme.

### Conflicts of Interest

Dr Susannah E. Murphy has received consultancy payments from p1Vital and has participated in paid speaking engagements for Lilly UK.

### References

1. Wang H, Dwyer-Lindgren L, Lofgren KT, *et al.* Age-specific and sex-specific mortality in 187 countries, 1970–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380, 2071–2094.
2. Kendler KS, Gardner CO, Neale MC, *et al.* Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? *Psychol Med*. 2001; 31, 605–616.
3. Boyce P, Parker G, Barnett B, *et al.* Personality as a vulnerability factor to depression. *Br J Psychiatry*. 1991; 159, 106–114.
4. Bruce ML. Psychosocial risk factors for depressive disorders in late life. *Biol Psychiatry*. 2002; 52, 175–184.
5. Kilzieh N, Rastam S, Maziak W, *et al.* Comorbidity of depression with chronic diseases: a population-based study in Aleppo, Syria. *Int J Psychiatry Med*. 2008; 38, 169–184.
6. Kessler RC, Magee WJ. Childhood adversities and adult depression: basic patterns of association in a US national survey. *Psychol Med*. 1993; 23, 679–690.
7. Kessler RC, Davis CG, Kendler KS. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. *Psychol Med*. 1997; 27, 1101–1119.
8. Briere J, Elliott DM. Prevalence and psychological sequelae of self-reported childhood physical and sexual abuse in a general population sample of men and women. *Child Abuse Negl*. 2003; 27, 1205–1222.
9. Lenze SN, Xiong C, Sheline YI. Childhood adversity predicts earlier onset of major depression but not reduced hippocampal volume. *Psychiatry Res*. 2008; 162, 39–49.
10. Rudolph K, Flynn M. Childhood adversity and youth depression: influence of gender and pubertal status. *Dev Psychopathol*. 2007; 19, 497–521.
11. Schilling EA, Aseltine RH Jr, Gore S. Adverse childhood experiences and mental health in young adults: a longitudinal survey. *BMC Public Health*. 2007; 7, 30.
12. O'Connor TG, Heron J, Glover V. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *J Am Acad Child Adolesc Psychiatry*. 2002; 41, 1470–1477.
13. Van den Bergh BR, Mulder EJ, Mennes M, *et al.* Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev*. 2005; 29, 237–258.
14. Talge NM, Neal C, Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry*. 2007; 48, 245–261.
15. Van den Bergh BRH, Van Calster B, Smits T, *et al.* Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: a prospective study on the fetal origins of depressed mood. *Neuropsychopharmacology*. 2007; 33, 536–545.
16. Barker DJ, Winter PD, Osmond C, *et al.* Weight in infancy and death from ischaemic heart disease. *Lancet*. 1989; 2, 577–580.
17. Barker DJ. Fetal origins of cardiovascular disease *Ann Med*. 1999; 31(Suppl. 1), 3–6.
18. Glover V. Annual research review: prenatal stress and the origins of psychopathology: an evolutionary perspective. *J Child Psychol Psychiatry*. 2011; 52, 356–367.
19. Jaddoe VWV, Troe E.-J.W.M., Hofman A, *et al.* Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the Generation R Study. *Paediatr Perinat Epidemiol*. 2008; 22, 162–171.
20. Misra DP, Nguyen RH. Environmental tobacco smoke and low birth weight: a hazard in the workplace? *Environ Health Perspect*. 1999; 107(Suppl. 6), 897–904.
21. Lieberman E, Gremy I, Lang JM, *et al.* Low birthweight at term and the timing of fetal exposure to maternal smoking. *Am J Public Health*. 1994; 84, 1127–1131.
22. Newton RW, Hunt LP. Psychosocial stress in pregnancy and its relation to low birth weight. *Br Med J*. 1984; 288, 1191–1194.
23. Brown SJ, Yelland JS, Sutherland GA, *et al.* Stressful life events, social health issues and low birthweight in an Australian population-based birth cohort: challenges and opportunities in antenatal care. *BMC Public Health*. 2011; 11, 196.

24. Bhagwanani SG, Seagraves K, Dierker LJ, et al. Relationship between prenatal anxiety and perinatal outcome in nulliparous women: a prospective study. *JAMA*. 1997; 89, 93–98.
25. Barker DJ. The developmental origins of adult disease. *J Am Coll Nutr*. 2004; 23(6), 588S–595S.
26. Huxley R, Owen CG, Whincup PH, et al. Is birth weight a risk factor for ischemic heart disease in later life? *Am J Clin Nutr*. 2007; 85, 1244–1250.
27. Barker DJ, Bagby SP, Hanson MA. Mechanisms of disease: in utero programming in the pathogenesis of hypertension. *Nat Clin Pract Nephrol*. 2006; 2, 700–707.
28. Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic review. *JAMA*. 2008; 300, 2886–2897.
29. Thompson C, Syddall H, Rodin I, et al. Birth weight and the risk of depressive disorder in late life. *Br J Psychiatry*. 2001; 179, 450–455.
30. Bellingham-Young DA, Adamson-Macedo EN. Foetal origins theory: links with adult depression and general self-efficacy. *Neuro Endocrinol Lett*. 2003; 24, 412–416.
31. Gale C, Martyn C. Birth weight and later risk of depression in a national birth cohort. *Br J Psychiatry*. 2004; 184, 28–33.
32. Alati R, Lawlor DA, Mamun AA, et al. Is there a fetal origin of depression? Evidence from the Mater University Study of Pregnancy and its outcomes. *Am J Epidemiol*. 2007; 165, 575–582.
33. Costello EJ, Worthman C, Erkanli A, et al. Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. *Arch Gen Psychiatry*. 2007; 64, 338–344.
34. Mallen C, Mottram S, Thomas E. Birth factors and common mental health problems in young adults: a population-based study in North Staffordshire. *Soc Psychiatry Psychiatr Epidemiol*. 2008; 43, 325–330.
35. Gudmundsson P, Andersson S, Gustafson D, et al. Depression in Swedish women: relationship to factors at birth. *Eur J Epidemiol*. 2011; 26, 55–60.
36. Osler M, Nordentoft M, Andersen AM. Birth dimensions and risk of depression in adulthood: cohort study of Danish men born in 1953. *Br J Psychiatry*. 2005; 186 400–403.
37. Raikkonen K, Pesonen AK, Kajantie E, et al. Length of gestation and depressive symptoms at age 60 years. *Br J Psychiatry*. 2007; 190, 469–474.
38. Inskip HM, Dunn N, Godfrey KM, et al. Is birth weight associated with risk of depressive symptoms in young women? Evidence from the Southampton Women's Survey. *Am J Epidemiol*. 2008; 167, 164–168.
39. Vasiliadis HM, Gilman SE, Buka SL. Fetal growth restriction and the development of major depression. *Acta Psychiatr Scand*. 2008; 117, 306–312.
40. Wojcik W, Lee W, Colman I, et al. Foetal origins of depression? A systematic review and meta-analysis of low birth weight and later depression. *Psychol Med*. 2012; 43, 1–12.
41. Haavind S, Bergin I, Brubakk AM. Mental health, school and leisure time of adolescents born “small for gestational age”. *Tidsskr Nor Laegeforen*. 2007; 127, 1933–1937.
42. Smith CA. The effect of wartime starvation in Holland upon pregnancy and its product. *Am J Obstet Gynecol*. 1947; 53, 599–608.
43. Stein AD, Ravelli AC, Lumey LH. Famine, third-trimester pregnancy weight gain, and intrauterine growth: the Dutch Famine Birth Cohort Study. *Hum Biol*. 1995; 67, 135–150.
44. Stein AD, Kahn HS, Rundle A, et al. Anthropometric measures in middle age after exposure to famine during gestation: evidence from the Dutch famine. *Am J Clin Nutr*. 2007; 85, 869–876.
45. Stein AD, Zybert PA, van der Pal-de Bruin K, et al. Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the Dutch Famine. *Eur J Epidemiol*. 2006; 21, 759–765.
46. Painter RC, de Rooij SR, Bossuyt PM, et al. Early onset of coronary artery disease after prenatal exposure to the Dutch famine. *Am J Clin Nutr*. 2006; 84 322–327, quiz 466–327.
47. Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. *Early Hum Dev*. 2006; 82 485–491.
48. Brown AS, van Os J, Driessens C, et al. Further evidence of relation between prenatal famine and major affective disorder. *Am J Psychiatry*. 2000; 157, 190–195.
49. Stein AD, Pierik FH, Verrips GH, et al. Maternal exposure to the Dutch famine before conception and during pregnancy: quality of life and depressive symptoms in adult offspring. *Epidemiology*. 2009; 20, 909–915.
50. Monk C, Georgieff MK, Osterholm EA. Research review: maternal prenatal distress and poor nutrition—mutually influencing risk factors affecting infant neurocognitive development. *J Child Psychol Psychiatry*. 2013; 54, 115–130.
51. Micali N, Stahl D, Treasure J, et al. Childhood psychopathology in children of women with eating disorders: understanding risk mechanisms. *J Child Psychol Psychiatry*. 2014; 55, 124–134.
52. Micali N, De Stavola B, Ploubidis GB, et al. The effects of maternal eating disorders on offspring childhood and early adolescent psychiatric disorders. *Int J Eat Disord*. 2013.
53. O'Connor TG, Heron J, Golding J, et al. 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.
54. Field T. Prenatal depression effects on early development: a review. *Infant Behav Dev*. 2011; 34, 1–14.
55. Pawlby S, Hay D, Sharp D, et al. Antenatal depression and offspring psychopathology: the influence of childhood maltreatment. *Br J Psychiatry*. 2011; 199, 106–112.
56. Pearson RM, Evans J, Koundali D, et al. Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at 18 years. *JAMA Psychiatry*. 2013; 70, 1312–1319.
57. Hellemans KGC, Sliwowska JH, Verma P, et al. Prenatal alcohol exposure: fetal programming and later life vulnerability to stress, depression and anxiety disorders. *Neurosci Biobehav Rev*. 2010; 34, 791–807.
58. Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neuropsychol Rev*. 2011; 21, 81–101.
59. Famy C, Streissguth AP, Unis AS. Mental illness in adults with fetal alcohol syndrome or fetal alcohol effects. *Am J Psychiatry*. 1998; 155, 552–554.
60. O'Connor MJ, Kasari C. Prenatal alcohol exposure and depressive features in children. *Alcohol Clin Exp Res*. 2000; 24, 1084–1092.
61. O'Connor MJ, Paley B. The relationship of prenatal alcohol exposure and the postnatal environment to child depressive symptoms. *J Pediatr Psychol*. 2006; 31, 50–64.

62. Barr HM, Bookstein FL, O'Malley KD, *et al.* Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring. *Am J Psychiatry.* 2006; 163, 1061–1065.
63. Liu T, Gatsonis CA, Baylin A, *et al.* Maternal smoking during pregnancy and anger temperament among adult offspring. *J Psychiatr Res.* 2011; 45, 1648–1654.
64. Cornelius MD, De Genna NM, Leech SL, *et al.* Effects of prenatal cigarette smoke exposure on neurobehavioral outcomes in 10-year-old children of adolescent mothers. *Neurotoxicol Teratol.* 2011; 33, 137–144.
65. Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Arch Gen Psychiatry.* 1998; 55, 721–727.
66. Menezes AM, Murray J, Laszlo M, *et al.* Happiness and depression in adolescence after maternal smoking during pregnancy: birth cohort study. *PLoS One.* 2013; 8, e80370.
67. Goldschmidt L, Richardson GA, Cornelius MD, *et al.* Prenatal marijuana and alcohol exposure and academic achievement at age 10. *Neurotoxicol Teratol.* 2004; 26, 521–532.
68. Gray KA, Day NL, Leech S, *et al.* Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age. *Neurotoxicol Teratol.* 2005; 27, 439–448.
69. Leech SL, Larkby CA, Day R, *et al.* Predictors and correlates of high levels of depression and anxiety symptoms among children at age 10. *J Am Acad Child Adolesc Psychiatry.* 2006; 45, 223–230.
70. Weinstock M. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Prog Neurobiol.* 2001; 65, 427–451.
71. Abe H, Hidaka N, Kawagoe C, *et al.* Prenatal psychological stress causes higher emotionality, depression-like behavior, and elevated activity in the hypothalamo-pituitary-adrenal axis. *Neurosci Res.* 2007; 59, 145–151.
72. Trezza V, Campolongo P, Cassano T, *et al.* Effects of perinatal exposure to delta-9-tetrahydrocannabinol on the emotional reactivity of the offspring: a longitudinal behavioral study in Wistar rats. *Psychopharmacology.* 2008; 198, 529–537.
73. O'Shea M, McGregor IS, Mallet PE. Repeated cannabinoid exposure during perinatal, adolescent or early adult ages produces similar longlasting deficits in object recognition and reduced social interaction in rats. *J Psychopharmacol.* 2006; 20, 611–621.
74. Levinson DF. The genetics of depression: a review. *Biol Psychiatry.* 2006; 60, 84–92.
75. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry.* 2000; 157, 1552–1562.
76. Caspi A, Sugden K, Moffitt TE, *et al.* Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003; 301, 386–389.
77. Ribeiro L, Busnello JV, Cantor RM, *et al.* The brain-derived neurotrophic factor rs6265 (Val66Met) polymorphism and depression in Mexican-Americans. *Neuroreport.* 2007; 18, 1291–1293.
78. Hek K, Demirkan A, Lahti J, *et al.* A genome-wide association study of depressive symptoms. *Biol Psychiatry.* 2013; 73, 667–678.
79. Lewis CM, Ng MY, Butler AW, *et al.* Genome-wide association study of major recurrent depression in the U.K. population. *Am J Psychiatry.* 2010; 167, 949–957.
80. Wray NR, Pergadia ML, Blackwood DH, *et al.* Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. *Mol Psychiatry.* 2012; 17, 36–48.
81. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, Ripke S, Wray NR, *et al.* A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry.* 2013; 18, 497–511.
82. Rice F, Harold GT, Boivin J, *et al.* The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. *Psychol Med.* 2010; 40, 335–345.
83. Leigh B, Milgrom J. Risk factors for antenatal depression, postnatal depression and parenting stress. *BMC Psychiatry.* 2008; 8, 24.
84. Champagne FA, Meaney MJ. Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. *Biol Psychiatry.* 2006; 59, 1227–1235.
85. Lewis SJ, Relton C, Zammit S, *et al.* Approaches for strengthening causal inference regarding prenatal risk factors for childhood behavioural and psychiatric disorders. *J Child Psychol Psychiatry.* 2013; 54, 1095–1108.
86. Owens M, Herbert J, Jones PB, *et al.* Elevated morning cortisol is a stratified population-level biomarker for major depression in boys only with high depressive symptoms. *Proc Natl Acad Sci U S A.* 2014; 111, 3638–3643.
87. Bhagwagar Z, Hafizi S, Cowen PJ. Increased salivary cortisol after waking in depression. *Psychopharmacology (Berl).* 2005; 182, 54–57.
88. Mannie ZN, Harmer CJ, Cowen PJ. Increased waking salivary cortisol levels in young people at familial risk of depression. *Am J Psychiatry.* 2007; 164, 617–621.
89. Portella MJ, Harmer CJ, Flint J, *et al.* Enhanced early morning salivary cortisol in neuroticism. *Am J Psychiatry.* 2005; 162, 807–809.
90. Bhagwagar Z, Hafizi S, Cowen PJ. Increase in concentration of waking salivary cortisol in recovered patients with depression. *Am J Psychiatry.* 2003; 160, 1890–1891.
91. Carnegie R, Araya R, Ben-Shlomo Y, *et al.* Cortisol awakening response and subsequent depression: prospective longitudinal study. *Br J Psychiatry.* 2014; 204, 137–143.
92. Strickland P, Morriss R, Wearden A, *et al.* A comparison of salivary cortisol in chronic fatigue syndrome, community depression and healthy controls. *J Affect Disord.* 1998; 47, 191–194.
93. Vreeburg SA, Hoogendijk WG, van Pelt J, *et al.* Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry.* 2009; 66, 617–626.
94. Doane LD, Mineka S, Zinbarg RE, *et al.* Are flatter diurnal cortisol rhythms associated with major depression and anxiety disorders in late adolescence? The role of life stress and daily negative emotion. *Dev Psychopathol.* 2013; 25, 629–642.
95. Davis EP, Glynn LM, Waffarn F, *et al.* Prenatal maternal stress programs infant stress regulation. *J Child Psychol Psychiatry.* 2011; 52, 119–129.
96. Brennan PA, Pargas R, Walker EF, *et al.* Maternal depression and infant cortisol: influences of timing, comorbidity and treatment. *J Child Psychol Psychiatry.* 2008; 49, 1099–1107.
97. O'Connor TG, Ben-Shlomo Y, Heron J, *et al.* Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biol Psychiatry.* 2005; 58, 211–217.

98. Maccari S, Darnaudey M, Morley-Fletcher S, et al. Prenatal stress and long-term consequences: implications of glucocorticoid hormones. *Neurosci Biobehav Rev.* 2003; 27, 119–127.
99. Witzmann SR, Turner JD, Meriaux SB, et al. Epigenetic regulation of the glucocorticoid receptor promoter 1(7) in adult rats. *Epigenetics.* 2012; 7, 1290–1301.
100. Liu D, Diorio J, Tannenbaum B, et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science.* 1997; 277, 1659–1662.
101. Weaver IC, Cervoni N, Champagne FA, et al. Epigenetic programming by maternal behavior *Nat Neurosci.* 2004; 7, 847–854.
102. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci.* 2009; 12, 342–348.
103. Oberlander TF, Weinberg J, Papsdorf M, et al. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics.* 2008; 3, 97–106.
104. Mairesse J, Lesage J, Breton C, et al. Maternal stress alters endocrine function of the feto-placental unit in rats. *Am J Physiol Endocrinol Metab.* 2007; 292, E1526–E1533.
105. Glover V, Bergman K, Sarkar P, et al. Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety. *Psychoneuroendocrinology.* 2009; 34, 430–435.
106. O'Donnell KJ, Bugge Jensen A, Freeman L, et al. Maternal prenatal anxiety and downregulation of placental 11beta-HSD2. *Psychoneuroendocrinology.* 2012; 37, 818–826.
107. Jensen Pena C, Monk C, Champagne FA. Epigenetic effects of prenatal stress on 11beta-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. *PLoS One.* 2012; 7, e39791.
108. Monk C, Myers MM, Sloan RP, et al. Effects of women's stress-elicited physiological activity and chronic anxiety on fetal heart rate. *J Dev Behav Pediatr.* 2003; 24, 32–38.
109. Giannakouloupoloulos X, Teixeira J, Fisk N, et al. Human fetal and maternal noradrenaline responses to invasive procedures. *Pediatr Res.* 1999; 45(Pt 1), 494–499.
110. Teixeira JM, Fisk NM, Glover V. Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. *BMJ.* 1999; 318, 153–157.
111. Stevens AD, Lumbers ER. Effects of intravenous infusions of noradrenaline into the pregnant ewe on uterine blood flow, fetal renal function, and lung liquid flow. *Can J Physiol pharmacol.* 1995; 73, 202–208.
112. Shnider SM, Wright RG, Levinson G, et al. Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. *Anesthesiology.* 1979; 50, 524–527.
113. Coe CL, Lubach GR, Karaszewski JW, et al. Prenatal endocrine activation alters postnatal cellular immunity in infant monkeys. *Brain Behav Immun.* 1996; 10, 221–234.
114. Kay G, Tarcic N, Poltyrev T, et al. Prenatal stress depresses immune function in rats. *Physiol Behav.* 1998; 63, 397–402.
115. Coe CL, Kramer M, Kirschbaum C, et al. Prenatal stress diminishes the cytokine response of leukocytes to endotoxin stimulation in juvenile rhesus monkeys. *J Clin Endocrinol Metab.* 2002; 87, 675–681.
116. Merlot E, Couret D, Otten W. Prenatal stress, fetal imprinting and immunity. *Brain Behav Immun.* 2008; 22, 42–51.
117. Couret D, Jamin A, Kuntz-Simon G, et al. Maternal stress during late gestation has moderate but long-lasting effects on the immune system of the piglets. *Vet Immunol Immunopathol.* 2009; 131, 17–24.
118. Diz-Chaves Y, Astiz M, Bellini MJ, et al. Prenatal stress increases the expression of proinflammatory cytokines and exacerbates the inflammatory response to LPS in the hippocampal formation of adult male mice. *Brain Behav Immun.* 2013; 28, 196–206.
119. Lefevre F, Moreau D, Semon E, et al. Maternal depression related to infant's wheezing. *Pediatr Allergy Immunol.* 2011; 22, 608–613.
120. Khashan AS, Wicks S, Dalman C, et al. Prenatal stress and risk of asthma hospitalization in the offspring: a Swedish population-based study. *Psychosom Med.* 2012; 74, 635–641.
121. Nielsen NM, Hansen AV, Simonsen J, et al. Prenatal stress and risk of infectious diseases in offspring. *Am J Epidemiol.* 2011; 173, 990–997.
122. Duijts L, Bakker-Jonges LE, Labout JA, et al. Perinatal stress influences lymphocyte subset counts in neonates. The generation R study *Pediatr Res.* 2008; 63, 292–298.
123. Wright RJ, Visness CM, Calatroni A, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med.* 2010; 182, 25–33.
124. O'Connor TG, Winter MA, Hunn J, et al. Prenatal maternal anxiety predicts reduced adaptive immunity in infants. *Brain, Behaviour, and Immunity.* 2013; 32, 21–28.