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Fetal origins of mental health: Evidence and mechanisms

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ABSTRACT

The concept of fetal programming states that changes in the fetal environment during sensitive periods of organ development may cause long-lasting changes in the structure and functioning of these organs later in life and influence the risk for chronic diseases such as coronary heart disease and type 2 diabetes. Fetal growth is a summary marker of the fetal environment and is reflected by relatively easy-to-obtain measures of size at birth such as birth weight. In the last two decades, a body of evidence emerged linking fetal growth with behavioural and mental health outcomes later in life. Cognitive functioning and behavioural problems in childhood, in particular inattention/hyperactivity, have been shown to be inversely related to fetal growth. Although results are mixed, risk for personality disorders and schizophrenia seems to be linked with fetal growth and adversity, while the evidence for mood disorders is weak. Vulnerability for psychopathology may also be influenced by prenatal adversity. There is evidence for associations of fetal growth with temperament in childhood as well as stress reactivity and distress. The associations of fetal growth with mental health later in life are potentially caused by specific prenatal factors such as maternal smoking, alcohol, toxins/drugs, nutrition, psychosocial stress and infection during pregnancy. The mechanisms likely involve changes in neurodevelopment and in the set point of neuroendocrine systems, and there is evidence that prenatal adversity interacts with genetic and postnatal environmental factors. Future studies should examine the effects of specific prenatal factors and attempt to disentangle genetic and prenatal environmental effects.

1. Introduction

The idea that prenatal events and maternal well-being during pregnancy may have long-lasting effects on the child's development is deeply rooted in diverse ancient cultures (see Ferreira, 1965, for a more detailed account of the history of beliefs about the importance of prenatal environmental factors). Studies published in the 1950s emphasised the long-term deleterious effects that complications of pregnancy and delivery, or the early social environment had on subsequent mental health, disability and behavioural problems. In subsequent decades these ideas fell out of fashion and it was considered that experiences at all ages were influential and the extent to which the effects of early adverse experience persisted depended on whether the early disadvantage was followed by later deprivation (Rutter and O'Connor, 2004). Since the 1990s, however, there has been a renewed interest in the idea that the early environment may have permanent and important effects and that these effects might be amplified by subsequent events. At that time epidemiological studies were showing strong links between measures of the quality of the prenatal environment such as birth weight and the risk of cardiovascular and metabolic disease (Barker, 1995b; Barker et al., 1993). In line with this notion, epidemiological studies also showed associations between early growth patterns and human behaviours or mental illnesses and it was tentatively suggested that these correlations could explain the known associations between cardiometabolic disease and psychopathology. Taken together with emerging animal evidence, there is now a compelling case that the early environment is specifically linked with impaired cognitive function, behavioural disorders especially hyperactivity/inattention and psychiatric conditions such as mood disorders and schizophrenia. The aims of this article are to review this evidence and discuss potential underlying mechanisms and methodological challenges.

2. The developmental origins hypothesis

Although it used to be thought that the developing fetus was largely protected from the environment, there is now much evidence that the fetus responds to environmental factors and one of the consequences are permanent changes in the structure and physiology of the offspring, which have been shown to increase

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the risk of major chronic diseases later in life, for example coronary heart disease and type 2 diabetes (Barker, 1995a). This process is termed fetal programming or developmental plasticity, and it is one of the core assumptions of the Developmental Origins of Health and Disease (DOHaD) model (Barker, 2004; Gillman, 2005; Gluckman and Hanson, 2004). In some instances these changes are adaptive, preparing individuals that are best suited to the environment forecast by the clues available in early life (Bateson et al., 2004). In other cases the effect of the early environment results in non-adaptive changes, for example as a result of physical or chemical constraints disrupting developmental processes.

2.1. Size at birth and fetal adversity

Because it is difficult to obtain reliable data about the nature of the fetal environment in human studies, many epidemiological studies have used easier-to-obtain measures based on birth outcomes such as birth weight. A few studies have used other measurements of size at birth such as length, head circumference, placental weight or ponderal index (kg/m^3; an indicator of thinness), but the extent to which these measurements add to birth weight is still not clear. It is generally recognised that these are crude measurements that only represent a summary measure of the success of fetal and infant development. One important issue is whether small size at birth is a result of growth retardation in term babies or prematurity, as their determinants may be different and they may have very different effects on subsequent health. Some studies do not have data on gestational age, while where this data is available it may be of variable quality being based, for example on the recalled date of the mother's last menstrual period.

Size at birth is the product of a fetus' trajectory of growth, which is set up at an early stage in development, and the materno-placental capacity to supply sufficient nutrients and oxygen to maintain that trajectory. Classical genetic factors play only a small part in the regulation of birth weight (Brooks et al., 1995; Lunde et al., 2007). While reduced fetal growth reflects fetal environmental adversity (meaning a suboptimal fetal developmental environment), it is a surrogate marker that itself is not causally linked with long-term effects on behaviour and mental health, complicating studies of fetal origins of adult health and disease (Gillman, 2002). As mentioned earlier, epidemiological studies often used measures of fetal growth as a marker of the fetal environment because it is difficult to obtain reliable and detailed data about the nature of the fetal environment in human studies. One important issue with the epidemiological literature is that the associations are graded across the birth weight range. Not all small babies develop mental health or behavioural problems and the proportion affected generally declines with increasing birth weight. In addition, birth weight or other measures of fetal growth are not linear measurements of developmental potential. For example babies born at the extremes of the birth weight distribution reflect different pathophysiological processes to babies whose weight variation is less extreme. Very low birth weight results from a range of serious materno-fetal pathologies, clinically recognisable as the syndrome of intrauterine growth retardation, which differ from the causes of variation in birth weight in the normal range. Fetal overgrowth or macrosomia is usually linked with maternal diabetes and is known to predispose to obesity, metabolic and vascular disease in later life (Dabelea et al., 2008). Consequently, many studies report inverse J-shaped or U-shaped relationships between measures of early growth and subsequent disease risk. However, despite the shortcomings of these measurements a body of evidence has emerged linking patterns of fetal growth with behavioural and mental health outcomes in later life which forms the basis of this review.

3. Size at birth and mental health

3.1. Cognitive functioning

Early case–control studies demonstrated a link between IQ and low birth weight, usually defined as the small fraction of children (<15%) of low birth weight compared with those of higher birth weight. A review of 10 studies found that all reported a decrement in IQ in low birth weight children which ranged from 3.8 points to 15.2 points difference between groups (Breslau, 1995). More recent studies have sought to evaluate whether the relationship holds across the range of birth weights or whether it is restricted to people who were unusually small at birth. The consensus from this research is that the relationship does hold across the range of birth weights but that the effect is modest (Shenkin et al., 2004). In a study of 4300 Danish military conscripts born between 1973 and 1975, Sorensen et al. found that the Boerge Prien IQ test increased progressively with birth weight levelling out above a birth weight of 4.2 kg (Sorensen et al., 1997). Other studies found similar results and showed that the effect was separate from that of social class and was observed within same sex sibships and could not therefore be explained by confounding by the family social environment (Matte et al., 2001; Shenkin et al., 2001). For example, a large-scale study of ~360,000 Swedish military conscripts showed that the association of fetal growth with cognitive functioning in adult life was similar within and between families, and that it was not explained by differences in socioeconomic status (Bergvall et al., 2006). Nevertheless, the effect of birth weight is much less than that of social class. In a study of the 1958 British Cohort Study of 10,845 boys and girls studied between the ages of 7 and 16 years, birth weight accounted for 0.5–1.0% of the variation in maths scores whereas social class accounted for 2.9–12.5% (Jefferis et al., 2002). Recently, a U-shaped association of fetal growth with the risk for intellectual disability in a large Australian cohort has been reported (Leonard et al., 2008). In studies where the effect of birth weight on cognitive function has been assessed throughout the lifecourse, the positive association between birth weight and cognitive function seems to decline with age. In the UK 1946 birth cohort study birth weight was associated with cognitive ability at age eight, was maintained during adolescence and early adulthood but was much weaker at age 43 (Richards et al., 2001).

3.2. Behavioural problems in children and adolescents

The case–control studies of children with low birth weight in comparison with normal birth weight controls also showed consistently increased hyperactivity and inattention, based on parental or teachers' assessments (Breslau et al., 1996; Indredavik et al., 2005, 2004; McCormick et al., 1996; Mick et al., 2002). In addition, a recent review summarised evidence for increased emotional problems in children born with low birth weight (Rice et al., 2007), and a longitudinal cohort study showed that the increased risk of low birth weight children for internalising and externalising problems was stable from childhood into early adulthood (Bohnert and Breslau, 2008). A number of studies have reported that the inverse effects of size at birth, for example birth weight, length and head circumference at birth, on behavioural problems extend over the full range of size at birth. Graded effects were found for hyperactivity/inattention, peer problems and antisocial behaviour (Kelly et al., 2001; Lahti et al., 2006; Linnet et al., 2006; Wiles et al., 2006). Similarly, children born small for gestational age (SGA) showed increased behavioural problems (Goldenberg et al., 1998; Hollo et al., 2002; Indredavik et al., 2005; O'Keeffe et al., 2003; Pryor et al., 1995; Zubrick et al., 2000), although the effects are often not strong (Indredavik et al., 2005) and not all studies confirmed these results (Sommerfelt et al., 2001). In line with the majority of the findings

from SGA studies, a number of studies demonstrated associations of fetal growth (i.e. size at birth adjusted for gestational age) with behavioural problems, in particular hyperactivity/inattention (Lahti et al., 2006; Linnet et al., 2006; Schlotz et al., 2008a; Wiles et al., 2006), conduct problems, peer problems and total behavioural difficulties (Schlotz et al., 2008a; Wiles et al., 2006). Associations of birth weight with behavioural problems later in life were also reported within twin-pairs, suggesting that the effect is independent of genetic inheritance (Hultman et al., 2007; van Os et al., 2001). When effects of birth weight were compared with effects of head circumference at birth, head circumference showed a stronger association with hyperactivity/inattention (Lahti et al., 2006; Schlotz et al., 2008a). Because head circumference is a good indicator of brain volume (Bartholomeusz et al., 2002), these findings suggest that it is altered brain development that is essential for the effect of fetal adversity on these behavioural problems.

Strikingly similar features are observed in animal models of rats that have been exposed to prenatal stress. The offspring show high anxiety-like behaviour and increased locomotor reactivity (Deminiere et al., 1992; Kapoor and Matthews, 2005; Vallee et al., 1997), suggesting that both externalizing and internalizing problems are associated with prenatal adversity.

3.3. Personality disorders

Personality disorder is defined as an enduring pattern of experience and behaviour that is stable over time, inflexible and deviates markedly from the expectations of the individual's culture (American Psychiatric Association, 2000). While there are no studies on fetal growth, two studies investigated associations of prenatal adversity with the risk for personality disorders in a cohort affected by the Dutch wartime famine. In 1944–45, the German army blockaded food supplies to punish the Dutch for assisting the allied invasion of Europe. The result was a 3-month famine made more severe by the unusually cold winter. Follow up of men and women who were in utero during the famine has revealed a wide variety of long term health effects of prenatal famine exposure. Neugebauer et al. (1999) found an increased risk for antisocial personality disorder (characterised by a disregard for, and violation of, the rights of others) in men that were exposed to the famine when their mothers were in the first or second trimester of pregnancy. These findings are in accordance with studies that showed associations of fetal adversity with antisocial behaviour problems in children reported in the previous section. In the same cohort, Hoek et al. (1996) found an increased risk for schizoid personality disorder (characterised by detachment from social relationships and a restricted range of emotional expression). This finding links with the studies on increased risk for schizophrenia reported in the following section and suggests that prenatal adversity may increase the risk for a broader category of schizophrenic spectrum mental disorders.

3.4. Schizophrenia

Schizophrenia is thought to be a complex neurodevelopmental disorder with a prevalence of approximately 1% in adult western populations (Mueser and McGurk, 2004). Its pathogenesis is still poorly understood. There is evidence for genetic susceptibility but it has become clear that adverse environmental exposures occurring both prenatally and postnatally which affect neurodevelopment play an important role (Mueser and McGurk, 2004). There is evidence that schizophrenics have delayed motor development and lower educational achievement before the onset of the disease (Jones et al., 1994). Together with the evidence for histopathological alterations in the cerebral cortex, cerebellar vermis, limbic system, and brain stem, as well as the problems of cerebral asymmetry, these findings are suggestive of a developmental component to the disease (Kovelman and Scheibel, 1986). A meta-analysis found that low birth weight, amongst other obstetric complications, is an important risk factor for the development of schizophrenia later in life (Cannon et al., 2002).

In a large population-based cohort study comprising births at Helsinki University Central Hospital from 1924 to 1933, Wahlbeck et al. (2001) showed that schizophrenia was linked with low late pregnancy maternal body mass index, low birth weight, shortness at birth and low placental weight. In childhood, persons who later developed schizophrenia were lean. Leaness in childhood was an independent additive risk factor to being small at birth. The data in this study suggested that the risk of schizophrenia increased by nearly 50% per kilogram decrease in birth weight. These findings are broadly supported by studies of a large cohort of 246,655 Swedish male conscripts, born in 1973–1980. However, the authors found a reverse J-shaped association between gestation-adjusted birth weight and schizophrenia with a 7-fold increase in risk amongst men of low birth weight (<2.5 kg) and a 3-fold increase in risk for those of high birth weight (>4.0 kg) (Gunnell et al., 2003). An examination based on the Swedish Twin Register has suggested that the effects of fetal growth restriction seem to operate within pairs of identical twins suggesting that the effect of fetal growth restriction is independent of genetic factors (Nilsson et al., 2005).

Studies of the Dutch wartime famine suggest a link with schizophrenia. Men and women conceived at the height of the famine had a 2-fold increase in risk of schizophrenia (Susser et al., 1996; Susser and Lin, 1992). This finding was replicated in a study of effects of exposure to the Chinese famine of 1959–1961 (St Clair et al., 2005). Prenatal famine exposure in patients with schizophrenia was also associated with decreased intracranial volume and an increase in brain abnormalities, predominantly white matter hyperintensities (Hulshoff Pol et al., 2000).

However, the results in this area are still mixed with some but not other studies confirming these observations. For example, a large scale Swedish cohort study found little evidence for an association of birth weight with schizophrenia later in life, although there was some association with length at birth (Gunnell et al., 2005). Although there is a significant increase in the relative risk, the absolute increase in risk for schizophrenia associated with low birth weight is rather small.

3.5. Mood disorders

The aetiology of depression is still incompletely understood. Adverse life events often precede the disease but act selectively in susceptible individuals (Hammen, 2005). Although a genetic predisposition for this susceptibility is postulated the genetic contribution is not high. A recent study of a large Swedish twin series shows that the heritability for depression is 29% in males, but 42% in females (Kendler et al., 2006). There is now increasing evidence that the early environment may be an important factor in predisposing to depressive illness. The first evidence for this came from the Dutch Winter Famine study which showed that second or third trimester exposure to famine was associated with an increased risk of admission for mood disorders in later life (Brown et al., 1995, 2000c). Evidence linking mood disorders with early growth came from a study of death certificates to identify cases of suicide in a cohort born during 1911–1930 in Hertfordshire, England. This study found that the mortality rate for suicide was higher in those who were lighter at one year of age (Barker et al., 1995). In addition, a large study that utilized data from combined Swedish registers found an inverse association of birth weight, adjusted for gestational age, with suicide later in life (Mittendorfer-Rutz et al., 2004). Because the number of suicide attempts is increased in mood disorders (Chen and Dilsaver, 1996) (although there are

other risk factors for suicide), these observations suggested that mood disorders themselves might be associated with abnormal early growth patterns. This was confirmed by a study of the prevalence of depression using the Geriatric Depression Scale in 882 men and women in the Hertfordshire cohort. In men the risk of depression was 3-fold higher in those born with birth weights less than 6.5 pounds compared with men who were 8.5 pounds or more at birth. No association was found in women (Thompson et al., 2001). Somewhat contrasting results were reported in the 1970 British Cohort Study. In this longitudinal study of births during one week in 1970, follow up studies of the prevalence of depression were carried out at age 16 and age 26 using the General Health Questionnaire and the Malaise Inventory, respectively. At age 26 women who were small at birth (<3.5 kg) had a 1.3-fold increased risk of depression compared with those who were heavy at birth (>3.5 kg). However there were no associations at age 16 and no trends in men at either age (Gale and Martyn, 2004). Similar results were obtained in an Australian prospective birth cohort, the Mater University Study of Pregnancy and its outcomes (Alati et al., 2007). Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale amongst 3719 participants at the 21-year follow up in 2002–2005. In multivariate analyses, there were a weak inverse association between birth weight and symptoms of depression in the whole cohort and some evidence of sex differences in this association. Amongst females, there was a graded inverse association: In the fully adjusted model, the odds ratio for a high level of depressive symptoms for a one standard deviation increase in birth weight was 0.82. Amongst males, there was no association. Recently, Costello et al. (2007) found that prenatal adversity was a significant risk factor for depression in adolescent girls. Moreover, this study demonstrated that prenatal adversity was a primary risk factor that was stable even when adjusting for various postnatal adverse environmental factors. However, a number of studies showed no association. In a cohort of 10,753 male singletons born in Copenhagen, Denmark in 1953 and for whom birth certificates had been traced in 1965 were followed from 1969 until 2002, there was no association between birth weight and admission to a psychiatric ward with a discharge diagnosis of depression (Osler et al., 2005). In a cohort of 8339 male and female adults born in Finland, high birth weight (>4500 g) was associated with a higher risk for depression at age 31 in women, while lower birth weight was not associated with an increased risk in men or women (Herva et al., 2008). Studies on associations of fetal growth with bipolar disorder later in life generally found inconsistent results, but most did not show an association, for example a large Danish study (Ogendahl et al., 2006). In summary, these findings suggest that associations between fetal growth and mood disorders are fairly weak and show inconsistent and unexplained gender differences.

3.6. Vulnerability to psychopathology

3.6.1. Temperament

The concept of temperament is based on the assumption that there are stable individual differences in behaviour, reactivity and self-regulation, and that these differences are partly constitutionally based or attributable to innate biological factors, with experience and maturation also being influential factors (Clark and Watson, 1999; Kagan and Snidman, 2004; Rothbart and Bates, 2006). Temperamental differences can be observed very early in life and are associated with risk for psychopathology later in life, in particular emotional disorders (anxiety and depression) and disruptive disorders such as conduct disorder and ADHD (Caspi and Shiner, 2008; Nigg, 2006).

In recent years, an increasing number of studies reported evidence for associations of fetal growth with temperament and personality characteristics. For example, restricted fetal growth has been associated with duration of orienting and activity level in 6-months-old infants (Roza et al., 2008). However, the association with activity level fell short of significance after adjustment for factors that indicate genetic factors (e.g. mother's height) and continuing adversity (e.g. socioeconomic status). Pesonen et al. (2006) reported associations of length at birth and ponderal index, adjusted for gestational age, with Negative Affectivity as measured by the Children's Behaviour Questionnaire (CBQ) in 5-year-old children. There was some indication of a curvilinear effect, with higher Negative Affectivity in those children that were born relatively short or long. Moreover, birth weight was inversely associated with Negative Affectivity only in those children that were born between 37 and 39 weeks' gestation. In a large cohort of over 60-year-old adults born in Helsinki, Finland, Raikkonen et al. (2008) found inverse associations of birth weight with hostility. However, increased hostility seemed to be largely confined to the participants with low birth weight (<2.5 kg). In the same cohort, Lahti et al. (2008) found curvilinear associations of fetal growth with Harm Avoidance as measured by the Tridimensional Personality Questionnaire, where harm avoidance is defined as a "tendency to respond intensely to signals of aversive stimuli, thereby learning to inhibit behavior to avoid punishment, novelty, and frustrative nonreward" (Cloninger, 1987). The associations with fetal growth restriction were largely attributable to high scores on the subscales Fear of Uncertainty and Shyness with Strangers. Recently, Schlotz et al. (2008a) reported inverse associations of fetal growth with Effortful Control (the capacity to voluntarily regulate attention and behaviour, e.g. inhibit a dominant response and initiate a subdominant response according to situational demands) as measured by the very short form of the CBQ in 7- to 9-year-old children, but no associations with Extraversion/Surgency or Negative Affectivity. Moreover, this study showed that Effortful Control mediated the association between fetal growth and hyperactivity/inattention, suggesting a potential pathway via temperament, which may act as a vulnerability factor to behavioural problems. Taken together, these studies suggest that prenatal environmental factors affect the development of temperament traits.

3.6.2. Stress and distress

Stress reactivity, defined as the extent to which a person is likely to respond to a stressful event, provides a conceptual link of the effect of stressful environments on psychological and somatic distress (Schulz et al., 2005) and has been shown to be a vulnerability factor for physical (Boyce et al., 1995; Cohen and Hamrick, 2003) and mental disease (Myin-Germeys et al., 2003; Myin-Germeys and van Os, 2007). Similar to findings on effects of prenatal adversity on physiological stress reactivity (Phillips, 2007), a small number of studies reported associations with behavioural stress reactivity in two cohorts. In a cohort of 18-year-old boys who underwent a standardized interview to diagnose suitability for military combat duty in Sweden, it has been shown that psychological stress susceptibility as assessed by the interviewer was inversely and curvilinearly associated with birth weight and head circumference at birth (Nilsson et al., 2001) as well as with being born small for gestational age (Lundgren et al., 2001, 2003), and this association was independent of parental education (Nilsson et al., 2004). In another cohort, Schlotz et al. (2007) found an inverse association of size at birth, adjusted for gestational age, with lower limb movements in a stressful situation, but not in a non-stress situation, in 7- to 9-year-old children. These associations were confined to boys, and the Swedish studies investigated effects in boys only. Therefore, the evidence to date suggests associations of prenatal adversity with psychological stress reactivity in boys but not in girls.

The term *distress* includes negative affective and somatic symptoms like fear, anxiety, depression, tension, pain or fatigue that are common consequences of stress experiences. Increased distress is an indicator of increased psychosocial stress in everyday life (although levels of distress are also influenced by an individual's personality (e.g. Bolger and Schilling, 1991; Watson and Clark, 1984) and genetic makeup (e.g. Gunthert et al., 2007)). There is some evidence of increased psychological distress in children born at a low birth weight. For example, Cheung (2002) found in the 1970 Birth Cohort Study an inverse J-shaped association of birth weight adjusted for gestational age (i.e. fetal growth) with the number of psychological symptoms of distress at age 26 years as measured by the Malaise Inventory, with the lowest psychological distress reported by those participants that were born at a normal birth weight. However, there were no associations with somatic distress. These results were confirmed using data from the National Child Development Study, where Cheung et al. (2002) found an inverse linear association of fetal growth with the number of psychological symptoms at age 23, 33 and 42 years. Again, there was no association of fetal growth with somatic symptoms of distress. Using the Aberdeen Children of the 1950s cohort, Wiles et al. (2005) found increased odds of psychological distress, as measured by four items of the General Health Questionnaire, for adults at age 45–51 years that had a low birth weight for gestational age (i.e. restricted fetal growth). All of these associations of psychological distress with fetal growth were stable when adjusted for socioeconomic status to control for effects of continuing adversity after birth. These results suggest that prenatal adversity increases the risk for experiencing negative emotional states, very likely as a consequence of stressful events.

4. Factors and mechanisms

As mentioned earlier, size at birth is only a surrogate marker of the fetal environment. Consequently, more recent epidemiological studies have sought to evaluate the effect of specific pregnancy exposures, such as smoking, stress or nutrition, on subsequent disease risk. This is likely to be a more useful approach, as it will indicate where interventions to improve maternal and child health could have long-term benefits. Fig. 1 summarises the principal factors, effects, pathways and confounders underlying the associations of fetal adversity with mental health.

4.1. Specific prenatal factors

Some of the relevant factors are related to the mother's health behaviour during pregnancy, in particular nutrition, smoking and drinking alcohol, as well as with stressful events in the mother's environment (see Fig. 1). They have consequences for the fetal environment either indirectly by altering the oxygen and nutrition supply to the fetus due to the placental vasoconstrictive action of stress hormones or toxins like nicotine, or directly by transfer of maternal glucocorticoids or other agents across the placenta (Holmes et al., 2006; Matthews and Phillips, 2006; Sarkar et al., 2008; Van den Bergh et al., 2005b; Wadhwa, 2005), and are associated with fetal growth. For example, psychosocial stress (Diego et al., 2006; Glynn et al., 2001; Khashan et al., 2008b; Lobel et al., 2008; Lou et al., 1994; Rondó et al., 2003), maternal diet (Andreasyan et al., 2007; Godfrey et al., 1996) and smoking during pregnancy (Lobel et al., 2008) have been shown to affect fetal growth. The similarities in the effects on birth weight at least in part seems to be due to changes in health behaviour in association with stress in pregnant women (Lobel et al., 2008; Schempf et al., 2009). These findings clearly suggest that differences in fetal growth are to a considerable extent due to effects of different adverse prenatal environmental factors. This is consistent with studies showing that the genetic effect on fetal growth is modest (Brooks et al., 1995; Lunde et al., 2007), although fetal growth certainly is not completely independent of genetic factors (Dunger et al., 1998; Kaku et al., 2007; Ong et al., 2004).

In line with their associations with fetal growth, specific prenatal factors are prominent risk factors for behavioural problems and mental health impairment in the offspring later in life. For example, smoking of the mother during pregnancy has been linked with behavioural problems in childhood and adolescence, including ADHD, aggression, conduct problems and depression (Ashford et al., 2008; Braun et al., 2006; Fergusson et al., 1998; Huijbregts et al., 2007; Indredavik et al., 2007; Linnet et al., 2005; Robinson et al., 2008; Rodriguez and Bohlin, 2005; Schmitz et al., 2006; Thapar et al., 2003; Wakschlag et al., 2006; Weissman et al., 1999),

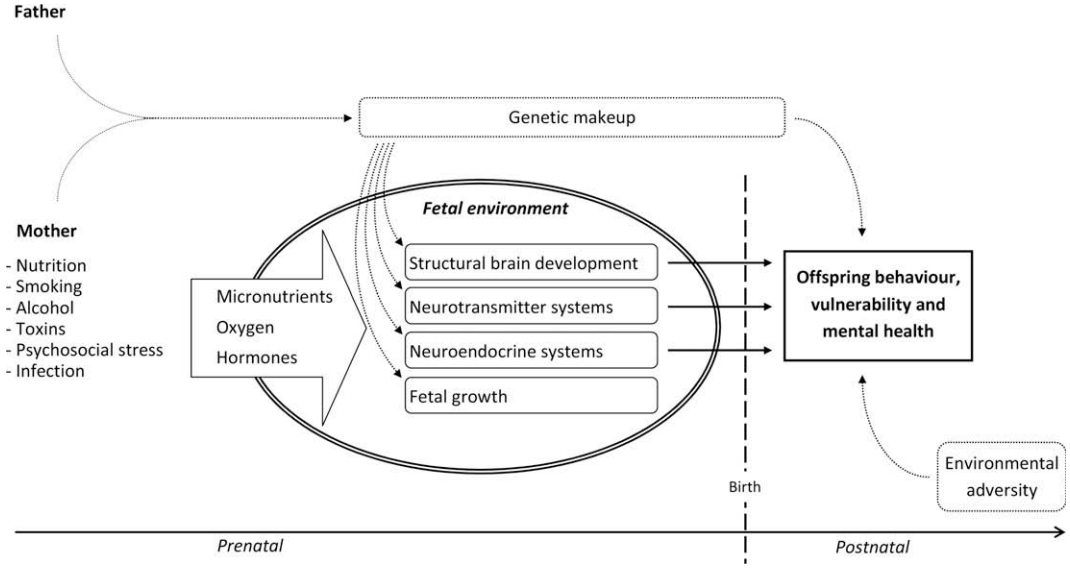

Fig. 1. A schematic summary of the principal factors, effects, pathways and confounders underlying the associations of fetal adversity with mental health. The principal pathway from specific maternal factors during pregnancy to increased risk of maladjusted behaviour, vulnerability, and mental health problems via fetal adversity is represented by solid boxes and arrows. Dashed boxes and arrows represent additional influences that act at different stages of the pathway.

more difficult temperamental characteristics in infancy (Kelmanson et al., 2002; Pickett et al., 2008) and cognitive function of the offspring (Mortensen et al., 2005; Olds et al., 1994). Recent studies showed that such effects are influenced by confounding maternal factors (Batty et al., 2006; Maughan et al., 2004), thus emphasising the importance of elaborate designs in studies of associations of prenatal smoking with long-term mental health effects in the offspring.

A number of studies reported that prenatal alcohol exposure increased the risk for behavioural problems, cognitive deficits and stress reactivity (Haley et al., 2006; Sayal et al., 2007; Sood et al., 2001; Streissguth et al., 1990), in particular after heavy levels of prenatal alcohol exposure (Fryer et al., 2007; Streissguth et al., 1991). However, evidence for an association with ADHD seems to be more equivocal (Linnet et al., 2003), and a potential pleiotropic genetic effect has been suggested (Knopik et al., 2006).

There is also evidence for an increased risk of behavioural problems and cognitive deficits after prenatal exposure to drugs like cocaine (Bada et al., 2007; Bennett et al., 2008; Singer et al., 2004) and marijuana (Goldschmidt et al., 2008; Huizink and Mulder, 2006).

Nutritional is an important factor in brain development (Georgieff, 2007), and there is accumulating evidence that maternal gestational status of micronutrients such as iron, fatty acids and folate as well as fish intake during pregnancy may have long-term consequences for behavioural problems and cognitive function later in life (Colombo et al., 2004; Gale et al., 2008; Hibbeln et al., 2007; Parsons et al., 2008; Schlotz et al., submitted for publication; Zhou et al., 2006).

A number of studies now reported effects of stress during pregnancy on behavioural outcomes like temperament, behavioural problems and cognitive function (Bergman et al., 2007; Gutteling et al., 2005, 2006; O'Connor et al., 2002; Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2005a, 2006), as well as increased risk for schizophrenia (Khashan et al., 2008a; Selten et al., 1999; van Os and Selten, 1998), autism (Beversdorf et al., 2005; Kinney et al., 2008) and depression (Watson et al., 1999). This research has been repeatedly summarised (e.g. Talge et al., 2007).

Finally, there is increasing evidence that prenatal infection increases the risk of schizophrenia later in life (Brown, 2006; Brown et al., 2004, 2000a,b; Mednick et al., 1988; Suvisaari et al., 1999).

In general, associations of fetal growth with behaviour and mental health are likely to be caused by one or more of these factors. Although not all of these specific factors are associated similarly with all of the outcome variables, the pattern of associations does not suggest highly selective effects of specific factors. For example, it is remarkable that very different factors like prenatal smoking and stress show very similar patterns of increased risk for behavioural problems. This may be due to similar transplacental mechanisms that may lead to similar neurodevelopmental alterations, and it corroborates the usefulness of fetal growth as a summary measure of fetal adversity. However, some of these factors may be related to offspring mental health and behaviour in the absence of an association with fetal growth. Moreover, in spite of similarities of effects, the precise alterations of brain development are likely to be different for different specific factors. Therefore, it is necessary to investigate more directly effects of specific determinants of postnatal outcomes. In addition, future studies should investigate the pathways underlying these effects, in particular the role of alterations in brain development and neuroendocrine system activity and reactivity.

4.2. Neurodevelopmental effects of prenatal adversity

An adverse or suboptimal fetal environment may cause irreversible changes in the brain that produce an effect specific to the maturational stage and kind of insult (Andersen, 2003; Levitt, 2003; Rice and Barone, 2000). There are well-described mechanisms that link fetal environmental factors such as hypoxia or stress with alterations in fetal brain development (e.g. Holmes et al., 2006; Rees and Harding, 2004). A number of human studies similarly support the assumption of a mediating role of brain development, for example the prenatal cephalisation index has been found to predict IQ deficits in childhood (Leitner et al., 2007), intrauterine growth restriction was associated with neuropsychological deficits suggestive of frontal lobe dysfunction (Geva et al., 2006), and fetal head growth has been shown to predict individual differences in temperament and hyperactivity/inattention (Schlotz et al., 2008a). A recent study linked antisocial behaviour in adolescence with fetal adversity (as indicated by birth weight, head circumference and Apgar scores at birth) via a pathway that includes neurological abnormalities in infancy and cognitive impairments in early childhood (Nomura et al., 2008), demonstrating the mediating role of early brain development. In addition, there is some evidence from neurodevelopmental studies. For example, a morphometric analysis based on cerebral magnetic resonance imaging (MRI) of children born small for gestational age demonstrated a significantly reduced total brain volume at 15 years of age (Martinussen et al., 2005). A study in infants reported negative associations of plasma tryptophan with the N1/P2 component of the auditory evoked potential, as well as differences between infants with intrauterine growth retardation and control infants, suggesting that the development of the serotonergic system in the brain might be associated with fetal growth (Manjarrez et al., 2005). Future neuroimaging studies could provide valuable insight into effects on specific brain areas and neurotransmitter systems of interest. Studies that investigated the effects of prenatal stress and hypoxia due to chronic placental insufficiency in rats, guinea-pigs, sheep and rhesus monkeys suggest the hippocampus, amygdala, basal ganglia, striatum, prefrontal cortex and cerebellum, amongst others, as specific regions of interest (Barros et al., 2006; Coe et al., 2003; Duncan et al., 2004; Fujioka et al., 2006; Mallard et al., 2000; Rehn et al., 2004; Salm et al., 2004; Van den Hove et al., 2006).

4.3. Neurodevelopmental damage or fetal programming?

It is likely that most of these mechanisms are non-adaptive and result in the birth of individuals who are not as well adapted to the environment as they could have been. An example would be perinatal hypoxic–haemodynamic encephalopathy as an aetiological model for ADHD (Lou, 1996). Because the striatum is at the circulatory watershed between the anterior and middle cerebral arteries it is particularly sensitive to cerebral ischaemia. Cerebral blood flow is often low in preterm infants because of deficient cerebral blood flow autoregulation. The subsequent damage to the striatal spiny cells leads to increased risk of hyperactivity, impulsivity and inattention. Although this is unlikely to account for the entire aetiology of ADHD and perinatal hypoxia also has been linked with other mental health outcomes, this model is a prototypical example for the possibility that neural damage rather than an adaptive response to the fetal environment underlies the long-term effects of fetal adversity.

Alternatively, a behavioural phenotype associated with prenatal adversity may have been evolutionary selected for if it conferred an adaptation to an adverse postnatal environment. For example, hyperactivity/inattention may be an indicator of a "response ready" trait, and a harsh, resource-depleted or rapidly changing environment might select for individuals with this adaptation (Jensen et al., 1997). Given that the finding of graded effects of fetal growth on hyperactivity/inattention is very consistent across studies, this may indeed represent a programming effect in that a "re-

sponse ready" trait may have been of advantage in an adverse ancient environment, whereas it is of disadvantage when the postnatal environment does not match the environment for which the organism was programmed. Indeed, this trait would be a disadvantage in an environment that demands attention and concentration in a classroom for achieving academic success. This concept parallels the mismatch concept of the DOHaD model, which states that a mismatch between the predictive adaptive response to adversity during prenatal development and the postnatal environment leads to disease and disadvantage (Gluckman and Hanson, 2004, 2005).

4.4. Changes in neuroendocrine systems

Recently there has been much interest in the possibility that the early environment may have long-term effects through resetting of a diverse array of hormonal systems that control growth and development. It has been known for a long time that the set point of these systems is plastic and can be programmed or permanently altered by events in utero or early infancy. Several neuroendocrine systems appear to be involved (see Phillips, 2002 for a review) but of particular importance is evidence that the major hormonal systems which mediate the stress response, including the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system, and the insulin-like growth factors are involved.

Animal studies show that the HPA axis can be altered or 'programmed' prenatally by nutrient restriction, maternal adversity or exposure to synthetic glucocorticoids, and postnatally by neonatal handling, maternal deprivation or infection (Matthews, 2002). The mechanisms underlying this phenomenon are thought to involve long-term changes in the expression of steroid receptors within the limbic system resulting from gene methylation (Weaver et al., 2004). There is now much human evidence that similar processes occur and are likely to be important in terms of long term health. For example, in two studies of boys and young men who were exposed to the Trier Social Stress Test (TSST; a psychological stress test involving a public speaking task and mental arithmetic), cortisol responses to stress exposure were significantly and inversely related to the subjects' birth weight (Jones et al., 2006; Wüst et al., 2005). These results are consistent with prenatal effects on psychological stress responses outlined above, because stress responses of the HPA axis and psychological stress responses are linked (Schlotz et al., 2008b). In girls and women, however, birth weight was associated with modulation of both sympathetic and parasympathetic function but not altered HPA function (Jones et al., 2007; Ward et al., 2004). There is ample evidence that chronic stress can lead to neurodevelopmental changes including changes in dendritic branching and hypertrophy, cell proliferation, and synaptic modelling leading to structural changes in brain areas that are important for cognitive and emotional functions, especially the hippocampus and amygdala (McEwen, 2003), and this may have long-lasting effects on behaviour and mental health (de Kloet et al., 2005; Gunnar and Quevedo, 2007). Detailed reviews of evidence and mechanisms can be found elsewhere (Owen et al., 2005; Talge et al., 2007; Weinstock, 2005).

However, it is also possible that the HPA axis and related neuroendocrine responses may be acting in a different and more subtle way to determine neurodevelopment. This insight into a possible alternative role of the HPA axis has emerged from 'life-history' theory in biology (Phillips, 2007). Life history theory describes the way in which organisms prioritize critical events or processes. These include the age at first reproduction, the effort expended in reproducing (for example, litter size and the number of reproductive events), length of life and the onset of senescence. These choices are made during development and usually involve 'trade-offs' such that the eventual phenotype is optimally adapted for the environment. Usually, the process involves resource allocation between three competing priorities: growth, reproduction and maintenance. Allocation of resources to one area, for example increased reproduction, will reduce the resources available for other processes such as longevity. A vivid example of this was a study of the British Monarchy which provided evidence that female longevity was negatively correlated with the number of progeny and positively correlated with age at first childbirth (Westendorp and Kirkwood, 1998). Every species appears to be distinctive in the way in which these trade-offs are carried out, but neuroendocrine processes appear to play a central role in most instances (see also Worthman and Kuzara, 2005). While the HPA axis has hitherto been viewed in terms of its function as a mediator of the classical stress response, it may well have an important role in directing resource partitioning during development amongst competing demands, leading to the development of different phenotypes according to the prevailing environmental conditions. Glucocorticoids regulate food intake and body weight and have a wide range of effects in multiple systems involved in growth, maintenance and reproductive strategy. Most information on the biology of the HPA axis derives from clinical studies using pharmacological quantities of glucocorticoids. As yet, we know relatively little as to how subtle changes in the HPA axis or the related sympathoadrenal system might affect the development of the phenotype. We also know little as to how this might be advantageous in adverse circumstances.

4.5. The influence of postnatal and genetic factors

Although there is clear evidence for associations of indicators of an adverse fetal environment with mental health traits it is necessary to take factors into account that are known to affect the outcomes and may also be associated with fetal adversity before conclusions about the significance of prenatal environmental effects can be drawn. Two main factors stand out in this regard, continuation of adversity in postnatal life and genetic factors.

4.5.1. Continuation of adversity

Environmental factors are known to affect the development of psychopathology during postnatal life, infancy and childhood (Rutter, 2005). Although the causal pathways are complex, a number of environmental characteristics are known to increase the risk for psychopathology, for example family conflict, maternal psychopathology, paternal criminality and low social class (Rutter and Quinton, 1977). There is also evidence that harsh, inconsistent parenting and exposure to acute and chronic stressors affect the behavioural adjustment of a child (McLoyd, 1998). To the extent that such environmental factors continue from prenatal to postnatal life they may confound fetal programming effects. For example, children's diets are often similar to those of their mothers (Robinson et al., 2007), thereby potentially providing a continuity of nutritional effects that span over prenatal and postnatal life. In this situation, a putative effect of prenatal nutrient supply of the fetus may actually be due to the child's diet, as dietary factors have been shown to affect behavioural problems in children (McCann et al., 2007; Wiles et al., 2007).

Associations of fetal growth or specific prenatal factors with mental health reflect long-lasting effects of prenatal adversity only if continuing adversity and postnatal environmental risk are taken into account. An approach here is to control for the socioeconomic status of the mother because adverse environmental factors tend to cluster in families with low socioeconomic status. However, because the socioeconomic status of the mother is related to the fetal environment, adjustment for socioeconomic status may conceal fetal effects. This may explain why some studies found that the association of prenatal adversity with mental health remained significant when adjusting for socioeconomic status (or other indicators of continuing adversity), while in others associations atten-

uated or disappeared. A number of studies indeed suggested interactions of postnatal environmental factors with effects of prenatal adversity on behaviour (Bergman et al., 2008; Bohnert and Breslau, 2008; Fan and Eaton, 2001; Gorman et al., 2001; Tully et al., 2004). In summary, the evidence supports the assumption of long-lasting effects of prenatal adversity on mental health and behaviour but also illustrates the importance of controlling for postnatal environmental adversity. Future studies should not only control for potential confounding factors, but also investigate the role that these factors may play in the pathway from prenatal adversity to mental health problems later in life.

4.5.2. Genetic factors

Genetic factors potentially confound associations between fetal adversity and behaviour or mental health. This is particularly important when predictor and outcome are similar, for example in studies on associations between maternal anxiety during pregnancy (an indicator of stress) and anxiety in the offspring later in life. Here, heritable genetic factors may contribute to the variation in anxiety, and therefore associations may be confounded by the shared genes between mother and child (Fig. 1). In addition to influencing fetal growth and neurodevelopment, as well as mental health outcomes, genes may similarly influence maternal health behaviour during pregnancy and the child's health behaviour later in life. This association increases the complexity of potential confounding of associations between prenatal adversity and mental health by heritable genetic factors.

Genetic and environmental effects can be disentangled by specific research designs. For example, twin studies have shown effects of fetal growth on behavioural problems that were not explained by shared genetic and environmental variance (Hultman et al., 2007; Rose, 2005; van Os et al., 2001). These studies strongly suggest that effects of fetal environmental adversity on behavioural problems later in life cannot be accounted for by genetic factors alone. A very interesting research design for disentangling genetic and prenatal environmental effects is based on assisted reproductive technologies. For example, there would be no genetic relationship between the intrauterine environment and the fetus when the egg or the embryo was donated, a situation that would allow separation of genetic and environmental effects (Thapar et al., 2007).

There is now increasing evidence of modulation effects of prenatal adversity on postnatal behaviour of the offspring by genetic factors (gene × prenatal environment interaction). For example, men (but not women) with the A2/A2 variant of the Taq1A polymorphism in the dopamine receptor D2 (DRD2) gene did not show a negative effect of fetal growth on educational attainment later in life (Keltikangas-Jarvinen et al., 2007). In a study on psychopathology, participants with the val/val variant of a polymorphism in the catechol-O-methyltransferase (COMT) gene were more susceptible to effects of prenatal adversity on postnatal antisocial behaviour (Thapar et al., 2005), while another study failed to replicate this finding (Sengupta et al., 2006). Another study found that maternal smoking during pregnancy and birth weight interacted with polymorphisms in the dopamine receptor D5 (DRD5) and the dopamine transporter (DAT1) genes in affecting antisocial behaviour of the offspring later in life (Langley et al., 2008). Interactions of dopamine receptor D4 (DRD4) and DAT1 polymorphisms with maternal smoking during pregnancy in affecting ADHD in the offspring were observed in one study (Neuman et al., 2007), while other studies failed to replicate the DRD4 finding (Altink et al., 2008; Langley et al., 2008).

Using a twin design, a negative gene × fetal growth interaction was demonstrated in addition to a main effect of fetal growth; additive genetic factors had less influence on postnatal behavioural problems in children with higher fetal growth restriction (Wichers et al., 2002). In summary, there is evidence that effects of prenatal adversity on postnatal behaviour exist independently of genetic factors, but some studies suggest gene × prenatal environment interactions affecting the behavioural outcome in the offspring later in life. The disentangling of genetic and fetal environmental factors should be a major topic of future research in this area. Because genes operate at every stage of the pathway (see Fig. 1) this will be a complex endeavour.

5. Conclusions

There is clear evidence for associations between fetal growth and mental health, and increasing evidence that behavioural dispositions that can act as vulnerability factors for the development of psychopathology, in particular temperament and behavioural stress reactivity, are affected as well. Most of the findings were robust when controlled for postnatal adversity (using socioeconomic status). A variety of specific prenatal factors such as exposure to maternal smoking, alcohol, cocaine, nutrients and psychosocial stress, have been associated with similar effects. In addition, there is evidence that the effects of fetal adversity on mental health are not due to genetic factors. Taken together, the findings suggest programming effects of a prenatal adverse environment on postnatal mental health and behaviour. Future studies should examine effects of specific prenatal factors and attempt to disentangle genetic and prenatal environmental effects. The findings are of relevance for public health, educational attainment and well-being. For example, health behaviour education of future mothers, reduction of stressful experiences and improvement of coping competencies during pregnancy could prevent behavioural problems and might increase health and well-being of their children later in life.

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