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Effects of perinatal mental disorders on the fetus and child

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Perinatal mental disorders are associated with increased risk of psychological and developmental disturbances in children. However, these disturbances are not inevitable. In this Series paper, we summarise evidence for associations between parental disorders and offspring outcomes from fetal development to adolescence in high-income, middle-income, and low-income countries. We assess evidence for mechanisms underlying transmission of disturbance, the role of mediating variables (underlying links between parent psychopathology and offspring outcomes) and possible moderators (which change the strength of any association), and focus on factors that are potentially modifiable, including parenting quality, social (including partner) and material support, and duration of the parental disorder. We review research of interventions, which are mostly about maternal depression, and emphasise the need to both treat the parent's disorder and help with associated caregiving difficulties. We conclude with policy implications and underline the need for early identification of those parents at high risk and for more early interventions and prevention research, especially in socioeconomically disadvantaged populations and low-income countries.

Introduction

A substantial body of evidence now exists that shows perinatal mental disorders are associated with an increase in a range of psychological and developmental disturbances in children. However, disturbances are not inevitable and effect sizes for these associations are mostly moderate or small. Therefore, why an association exists between a particular parental disorder and child outcome, and in what situations the risk is accentuated or ameliorated, is important to understand. Most investigators have tried to answer this question with attempts to elucidate possible mechanisms of transmission, that is, the role of mediating variables underlying associations between parent psychopathology and outcomes in their children, and possible moderators that change the strength of any association.

In this Series paper, we summarise the evidence about the different domains of development that are affected by perinatal mental disorders, and describe mediating and moderating variables, interventions, and implications of policies.

We mainly focus on depression and anxiety disorders during the perinatal period, but also assess the evidence for bipolar disorder, other psychoses, personality disorders, and eating disorders, although little research has been done about these disorders in relation to child outcomes. We prioritise findings from longitudinal studies (especially meta-analyses of such studies) for which, by contrast with cross-sectional designs, the temporal sequence of exposure and outcome is known. This knowledge helps to increase the potential for causal inference, although still not as clearly as experimental designs. We report evidence from studies that use reliable and valid measures of mental disorders of either interviews (providing categorical clinical diagnoses) or self-report symptom questionnaires. Questionnaires are feasible in large population-level studies, often have well established thresholds to suggest clinically significant levels of symptoms, and can be used as continuous scales. We take a developmental perspective, report associations between perinatal disorders and offspring outcomes, beginning with fetal and proceeding through to adolescent outcomes. Although the focus of this Series is maternal disorders, when deeming the effect on the child, paternal disorders also need to be taken into account.

Key messages

- Substantial global evidence exists that perinatal disorders are associated with risks for a broad range of negative child outcomes, which can persist into late adolescence
- However, risks are not inevitable and in the absence of severe or chronic maternal disorder or other adversities, the effect sizes are generally small or moderate
- Most research has focused on mothers, but growing evidence suggests that the fathers' mental health is also associated with child developmental disturbances
- Mechanisms underlying associations are complex and include a range of genetic, other biological, and environmental pathways
- Research should prioritise investigating the effectiveness of interventions in reducing risk to the child and reducing symptoms in the affected parent
- Parenting is a key modifiable pathway to explain some of the risks of perinatal disorders to the child and should be specifically targeted in interventions
- Interventions could be most important in the context of additional adversities, such as in socioeconomically disadvantaged populations, where risks to the child seem highest; where several risks are present and resources are scarce, especially in areas in low-income and middle-income countries, innovative strategies are needed

Fetal and neonatal outcomes

Two meta-analyses[1,2] have assessed the association between antenatal depression and fetal and neonatal outcomes. Both reports showed that symptoms of antenatal depression are associated with an increased risk for premature delivery (<37 weeks' gestation). One reported that studies controlling for women taking antidepressant drugs or smoking generated small (and non-significant) odds ratios,[1] whereas the second[2] concluded that "the summary relative risk was comparable for depressed women treated and not treated with antidepressants".[2] Antidepressants or smoking can be markers for more severe depression[3] and the effects of antenatal depression on prematurity (and low birthweight) were strong in studies where depression was defined by a disorder,[2] suggesting that severity of disorder is important.

A discrepancy was noted between the findings relating to depression and low birthweight; one meta-analysis[2] reported a modest association whereas the other reported a non-significant association.[1] However, in the meta-analysis reporting no association,[1] studies from low-income and middle-income countries (LMICs) were excluded from analyses. In geographically diverse studies incorporated within the second meta-analysis,[2] moderator analyses showed that the association with low birthweight was higher in LMICs than in high-income countries (HICs). Low birthweight might therefore be a substantial factor in LMICs, but not in HICs, except possibly in socio-economically disadvantaged communities.[2]

Antenatal depression was not associated with pre-eclampsia, Apgar scores, or admission to neonatal intensive-care units; for intrauterine growth restriction, antenatal depression was associated with an increased risk but only in LMICs.[1,2] Additional researchers in a meta-analytic review[4] examined associations between these outcomes and use of antidepressants during pregnancy, but reported weak associations after accounting for confounding.[4]

Some fetal and neonatal outcomes have been investigated mostly in association with the use of antidepressants rather than with a diagnosis of depression[4] usually because of the availability of prescription data in large population databases studies,[3] making it difficult to disentangle the effect of antidepressants, life style confounders, and depression.

Evidence is inconsistent for associations between antenatal anxiety and adverse fetal outcomes. A meta-analysis[5] reported small, non-significant correlations for most outcomes other than pregnancy-related anxiety and young gestational age at birth. A meta-analysis[6] in 2014 showed slight associations between anxiety and both preterm birth and low birthweight, although birthweight was not significant when regarding adjusted findings.[6] Both meta-analyses were limited by the paucity of studies and the frequent comorbidity of anxiety with depression and life stressors, which could confound associations.[7]

Other mental health problems during pregnancy have been associated with fetal and neonatal outcomes. Several studies suggest that maternal anorexia nervosa (active or past) is associated with low birthweight, although associations are inconsistent with high rates of prematurity.[8] Schizophrenia has also been associated with an increased risk of low birthweight, preterm delivery, stillbirth, and infant death within 1 year after birth.[9–11] This risk might be partly attributable to environmental factors associated with adversity, including smoking, poverty, poor nutrition, and substance misuse.[11] Risks of such adverse outcomes do not substantially differ between infants according to whether their mothers had a history of a psychiatric admission for schizophrenia or affective disorders. Risks for both groups with either schizophrenia or affective disorders are lower than they are for infants of mothers with substance misuse disorders.[12]

Infant, child, and adolescent outcomes
Overview
In view of the many studies that aim to examine associations between perinatal disorders and offspring outcomes, we structure this section by domain of development, reviewing findings associated with different disorders within each domain. Only recent HICs studies (2009–13) are included; however, in view of the paucity of LMICs studies, any study from these contexts were included (2000–13) in tables 1–5.

	Time of first exposure	Exposure measure (maternal)		Outcome measure (child)		Age of children at follow-up	Results	Strengths and limitations	
		Clinical interview or objective of assessment	Self-report	Objective assessment or interview	Questionnaire (parent or child reported)			Confounding variables included	Mediators or moderators
Gerardin 2011; n=164; France[13]	Antenatal	Clinical interviews, DSM-IV	Not reported	NBAS	ITSEA	12 months	Antenatal depression was associated with increased externalising and internalising symptoms on the ITSEA and poor motor and regulation skills on NBAS	None reported; however, exclusions for at risk pregnancies were made	Many associations limited to boy infants
Blair 2011; n=120; USA[14]	Antenatal	Not reported	STAI; PSA	Not reported	ECBQ	2 years	Child negative affectivity was associated with both the initial intercept and the trajectory of maternal PSA in pregnancy	Postnatal anxiety, maternal age, education, ethnic origin, marital status	Not reported
Velders 2011; n=2698; Netherlands (generation-R)[15]	Antenatal	Not reported	BSI	Not reported	CBCL (cutoff)	3 years	Child internalising behaviour was associated with antenatal depression (OR 1·18 [95% CI 1·08–1·29]; similar associations reported for anxiety symptoms)	Child sex, birthweight, birth order, ethnic origin, and age at questionnaire; maternal smoking and alcohol use during pregnancy, parental age, and parental level of education	Mediated by maternal depression at age 3 years and parental hostility
Davis 2012; n=178; USA[16]	Antenatal	Salivary cortisol	PSS; CES-D; STAI; PSA	Not reported	CBCL anxiety scale	6–9 years	Maternal antenatal pregnancy-specific anxiety score was associated with child CBCL score (β 0·22, p<0·05); maternal cortisol concentration was associated with CBCL score (β 0·16, p<0·05)	Child sex, gestational age at birth, maternal level of education, and maternal psychosocial stress at the time of child assessment	Not reported
Barker 2011; n=3298; UK (ALSPAC)[17]	Antenatal	Not reported	EPDS; CROWN-CRISP index	DAWBA; internalising disorders	Not reported	8 years	Child internalising behaviour was associated with antenatal anxiety (β 0·07, p<0·05) but not anetnatal depression; postnatal depression (β 0·08, p<0·05); postnatal anxiety (β 0·17, p<0·05)	Adjusted for cumulative risk score derived from SES, marital status, teenage mother, substance use, criminal background, antenatal and postnatal anxiety and depression were mutually adjusted	Not reported
Leis 2013; n=2891; UK (ALSPAC)[18]	Antenatal	Not reported	EPDS; CROWN-CRISP index	Not reported	SDQ mother and teacher report	10–11 years	Associations with total emotional SDQ score in the child; antenatal depression (β 0·22 [SE 0·07], p<0·001); antenatal anxiety (β 0·43 [SE 0·11], p<0·001); similar associations were noted for postnatal depression, but adjusted associations not given; no associations were reported for teacher-reported SDQ; similar associations reported for other SDQ subscales	Marital status, maternal age, birthweight, child sex, maternal education, alcohol use during pregnancy, offspring smoking, depression and anxiety, mutually adjusted and later symptoms were controlled for	Not reported
Pawlby 2009; n=127; UK[19]	Antenatal	Pregnancy: clinical interview schedule; at age 16 years: SADS-L	Not reported	Depression, diagnosis clinical interview DSM-IV, CAPA	Not reported	11 years and 16 years	Antenatal depression was associated with increased risk of depression for child at age 16 years (OR 4·70 [95% CI 1·60–13·86])	Family structure	Mediated by later chronic maternal depression after birth
Korhonen 2012; n=192; Finland[20]	Antenatal	Not reported	EPDS	Not reported	CBCL YSR	16 years or 17 years	Antenatal and postnatal depression symptoms were not associated with high internalising scores on the YSR or CBCL; however, antenatal and postnatal depression were associated with low social competence on CBCL and YSR	Later maternal depression at child age 16–17 years	Association between postnatal depression and social competence was only reported in boys and not in girls

(Table 1 continues on next page)

	Time of first exposure	Exposure measure (maternal)		Outcome measure (child)		Age of children at follow up	Results	Strengths and limitations	
		Clinical interview or objective of assessment	Self-report	Objective assessment or interview	Questionnaire (parent or child reported)			Confounding variables included	Mediators or moderators
(Continued from previous page)									
Pearson 2013; n=8937; UK[21]	Antenatal	Not reported	EPDS	Depression diagnosis clinical interview CIS-R, ICD10	Not reported	18 years	Association between 1 SD increase in maternal EPDS score and child depression at age 18 years: antenatal EPDS (OR 1·23 [95% CI 1·03–1·44]); postnatal EPDS in mothers with low education (OR 1·26 [1·06–1·50]) or high education (OR 1·09 [0·88–1·36])	Maternal age, social class, parity, history of depression before pregnancy, smoking during pregnancy, breastfeeding in the first year, use of non-parental child-care, later depression	Maternal education moderated the effects of postnatal but not antenatal depression
Reck 2013; n=82; Germany[22]	Postnatal	Clinical interviews, DSM-IV	Not reported	Still Face Paradigm, Cortisol reactivity in response to Still Face procedure*	Infant behaviour questionnaire temperament	3–8 months	Postnatal anxiety was associated with more distress to novelty and reported emotional problems	Sex of infant	Not reported
Bosquet Enlow 2011; n=52; USA[23]	Postnatal	Not reported	PTSD symptoms; PCL-C; EPDS	Observed emotion regulation, still face	ITSEA infant behaviour questionnaire	6 months and 13 months	Maternal PTSD symptoms were associated with infants' emotional regulation at age 6 months as assessed by infant ability to recover from distress and maternal report; maternal PTSD symptoms predicted maternal report of infant externalising, internalising, and dysregulation symptoms at age 13 months	Maternal age, educational attainment, maternal depression, marital status, parity, financial strain, race, and ethnic origin, infant's sex, birthweight, gestational age, race, and ethnic origin	Not reported
Feldman 2009; n=22 depressed, 19 anxious, and 59 controls; USA[24]	Postnatal	Depression and anxiety clinical interviews, DSM-IV	Not reported	Observed social engagement, fear regulation, cortisol	Not reported	9 months	Compared with controls, offspring of mothers with depression showed reduced social engagement, increased negativity, and poor fear regulation	None reported	Effects on social engagement were moderated by maternal sensitivity
Hartley 2010; n=83; South Africa[25]	Postnatal	Not reported	EPDS	Not reported	Modified alarm distress baby scale	10–12 months	No association between postnatal depression and social withdrawal	None reported	Sex of child, small sample size with depression (n=26), HIV sample
Conroy 2012; n=200; UK[26]	Postnatal	Clinical interview, DSM-IV SCID	Not reported	Not reported	ITSEA social and emotional (cutoffs)	18 months	Postnatal depression was associated with child ITSEA subscores for internalising (OR 6·86 [95% CI 1·34–35·14])	Occupation, ethnic origin, partner status, and later maternal depression, sex of infant	Moderated by comorbid personality disorders
Kersten-Alvarez 2012; n=142 (29 with depression, 113 controls; Netherlands[27]	Postnatal	Clinical interviews, DSM-IV	Not reported	Puppet interview (used to assess self esteem)	CBCL, internalising; PSBQ; teacher reported ego-resiliency: California Child Q-set†	Early school (children's average age of 5 years)	No evidence that postnatal depression was associated with internalising or low self-esteem, but was associated with low peer social competence and ego-resiliency	Child age, sex of child, maternal education, partner conflict, stressful life events, separation from father	Moderated by sex of the child; associations were stronger for girls than for boys
Verbeek 2012; n=2729; Netherlands[28]	Postnatal	Not reported	Maternal report interviewer led based on DSM-IV	Not reported	CBCL (parents and teachers)	10–15 years	Postnatal depression was associated with internalising symptoms (β 0·28 [95% CI 0·14–0·41], p<0·001)	Smoking or drinking during pregnancy, social-economic position, and obstetric factors	Not reported

(Table 1 continues on next page)

	Time of first exposure	Exposure measure (maternal)		Outcome measure (child)		Age of children at follow up	Results	Strengths and limitations	
		Clinical interview or objective of assessment	Self-report	Objective assessment or interview	Questionnaire (parent or child reported)			Confounding variables included	Mediators or moderators
(Continued from previous page)									
Naicker 2012; n=937; Canada (NLSCY)[29]	Postnatal	Not reported	CES-D-12	Not reported	Own scale based on DSM-III	12–13 years	Children exposed to maternal depression were at an increased risk of depression: first exposed to maternal depression postnatally (OR 1·36 [95% CI 0·80–2·32]) and exposed at age 2–3 years (OR 1·87 [1·05–3·53])	Life events, maternal alcohol use, child and maternal chronic health problems, marital status, household income, sex of child, later maternal depression	Not reported
Murray 2011; n=100; UK[30]	Postnatal and after	Clinical interviews, SPI	Not reported	Interview using KSADS	Not reported	16 years	Postnatal depression was associated with increased risk of offspring depression (OR 4·99 [95% CI 1·68–14·70])	Variables considered as mediators	Association partly mediated by marital conflict, maternal support, continued maternal depression, attachment security, and ego-resilience

OR=odds ratio. DSM=diagnostic and statistical manual. NBAS=neonatal behavioural assessment scale. ITSEA=infant toddler social emotional assessment. STAI=state-trait anxiety inventory. PSA=pregnancy related anxiety scale. ECBQ=early child behaviour questionnaire. BSI=brief symptom inventory (psychological symptoms). CBCL=child behavioural checklist (internalising and externalising symptoms). PSS=perceived stress scale. CES-D=centre for epidemiologic studies depression scale. EPDS=Edinburgh postnatal depression scale. DAWBA=development and well-being assessment. ALSPAC=Avon longitudinal study of parents and children (UK). SES=socioeconomic status. SDQ=strengths and difficulties questionnaire (internalising and externalising symptoms). SE=standard error. SADS-L=schedule for affective disorders and schizophrenia-lifetime. CAPA=child and adolescent psychiatric assessment. PTSD=post-traumatic stress disorder. PCL-C=post-traumatic stress disorder checklist. LMIC=low-income and middle-income countries. SCID=structured clinical interview for DSM-IV. PSBQ=preschool social behaviour questionnaire. SPI=standardised psychiatric interview. NLSCY=national ongitudinal survey of children and youth (Canada). KSADS=kiddie-schedule for affective disorders and schizophrenia. *The mother is requested to stop responding and show a blank, unresponsive face to the infacnt for a short duration and the infant's reaction is noted. †Personality dimensions, in Kersten-Alvarez[26] were used to assess ego-resiliency.

Table 1: Emotional outcomes

Emotional (internalising) difficulties and social development

Children's emotional and behavioural difficulties are often conceptualised as being either internalising or externalising. Internalising difficulties include symptoms or diagnoses of depression and anxiety (eg, separation anxiety and phobias). By social development, we refer to a child's development of social skills, such as perspective taking, empathy, and cooperation.

Longitudinal studies have shown that antenatal depression is associated with an increased risk for child emotional problems;[13,15,18] self-reported symptoms and depressive disorder are associated with an increased risk of clinical depression in late adolescence.[19,21]

Increased risks of emotional problems in children of mothers with postnatal depression have long been noted.[57] Detailed records of mother and infant behaviours showed that infants of mothers with postnatal depression have an increased risk of difficulties in early emotional regulation and social behaviour.[58,59] Longitudinal studies provide evidence for associations between postnatal depression and emotional outcomes across domains and age ranges, including internalising disorders, poor social competence in school years, and an increased risk of depression during adolescence (table 1).[25,27,28,30,59] Risks are associated with both symptoms of depression and depressive disorder, although effect sizes are generally large in children of mothers diagnosed with depressive disorder (table 1).

In view of the high extent of the association between depression in the antenatal and postnatal periods, large numbers of participants are required to provide sufficient power to assess whether the risks associated with antenatal and postnatal depression are independent of each other.[21,32] One study[21] reported independent associations between symptoms of antenatal and postnatal depression and offspring depression at age 18 years. Maternal level of education moderates the association between symptoms of postnatal but not antenatal depression, and offspring depression,[21] suggesting different mechanisms of risk are linked to antenatal and postnatal depression exposure.

Fewer investigations have been done to assess associations between antenatal and postnatal anxiety and child emotional difficulties than have for perinatal

	Time of first exposure	Exposure measure (maternal)		Outcome measure (child)		Age of children at follow-up	Results	Strengths and limitations	
		Clinical interview or objective assessment	Self-report	Objective assessment or interview	Questionnaire (parent or child reported)			Confounding variables included	Mediators or moderators
Pemberton 2010; n=361; USA[31]	Antenatal	Not reported	BDI	Not reported	CBCL	27 months	For the birth mother, prenatal–postnatal depressive symptoms were associated with externalising (β 0·09, p<0·10); for an adoptive mother postnatal depressive symptoms associated with child externalising (β 0·14, p=0·05)	Openness in adoption, sex of child, parent age, prenatal complications, birth; adoptive parent antisocial behaviour, and infant characteristics	Not reported
Velders 2011; n=2698; Netherlands (generation-R)[15]	Antenatal	Not reported	BSI	Not reported	CBCL	3 years	Evidence that child externalising difficulties were associated with antenatal depression (OR 1·19 [95% CI 1·09–1·30])	See table 1	Mediated by maternal depression at age 3 years and parental hostility
Van Batenburg-Eddes 2013; n=2280, Netherlands (generation-R); n=3442, UK (ALSPAC)[32]	Antenatal	Not reported·	EPDS	Not reported	SDQ, CBCL	3 years	Child attention problems were associated with antenatal depression: generation-R (OR 1·23 [95% CI 1·05–1·43]; ALSPAC (OR 1·33 [1·19–1·48]); and antenatal anxiety: generation-R (OR 1·24 [1·06–1·46]); ALSPAC (OR 1·32 [1·19–1·47])	Sex of child, birthweight, birth order, ethnic origin, and age at questionnaire; maternal smoking and alcohol use during pregnancy, and maternal level of education; family income; and adjusted for depression or anxiety of a partner during pregnancy	After adjusting for maternal symptoms after birth, antenatal maternal depression and anxiety were no longer associated with child attention problems in generation-R
Barker 2011; n=3298; UK (ALSPAC)[17]	Antenatal	Not reported	EPDS CROWN-CRISP index	DAWBA: externalising disorders	Not reported	8 years	Child externalising behaviour was associated with antenatal depression (no association with anxiety; β 0·09, p<0·05); and postnatal depression (β 0·09, p<0·05)	Adjusted for a cumulative risk score derived from SES, marital status, teenage mother, substance use, criminal background, and antenatal and postnatal anxiety and depression, mutually adjusted	Not reported
Korhonen 2012; n=192; Finland[20]	Antenatal	Not reported	EPDS	Not reported	CBCL, YSR	16–17 years	Antenatal and postnatal depression was associated with higher externalising score on the YSR, but not the CBCL	Later maternal depression at child age of 16–17 years	Association between postnatal but not antenatal depression was stronger in boys than in girls; prospective
Hay 2010; n=120; UK[33]	Antenatal	Clinical interview, ICD-9 CIS	Not reported	DSM-IV; conduct disorder or antisocial behaviour	Not reported	16 years	Associations between antenatal depression and offspring antisocial behaviour (OR 2·46 [95% CI 1·1–5·48])	Associations were similar when including antenatal anxiety, smoking, drinking, postnatal and later depression, and social adversity	Associations between antenatal depression and offspring antisocial behaviour were reduced when maternal conduct disorder was adjusted for
Conroy 2012; n=200; UK[26]	Postnatal	Clinical interview, DSM-IV	Not reported	Not reported	ITSEA (SD 9)	18 months	Postnatal depression was associated with infant dysregulated behaviour (β 5·12 [95% CI 1·49–8·75])	Occupation, ethnic origin, partner status, later maternal depression, sex of infant, maternal sensitivity towards their infant	Moderated by comorbid personality disorder
Galera 2011; n=2057; Canada[34]	Postnatal	Not reported	CES-D scale	Not reported	Not reported	17 months to 8 years, trajectories of ADHD symptoms	Postnatal depression was associated with an increased risk of high trajectories of hyperactivity–impulsivity and inattention symptoms through childhood (OR 1·35 [95% CI 1·18–1·54])	Prematurity and birthweight of child; prenatal smoking, drug and alcohol use; family structure, maternal age, income, maternal education, parenting factors, and paternal depression	Not reported

(Table 2 continues on next page)

	Time of first exposure	Exposure measure (maternal)		Outcome measure (child)		Age of children at follow-up	Results	Strengths and limitations	
		Clinical interview or objective assessment	Self-report	Objective assessment or interview	Questionnaire (parent or child reported)			Confounding variables included	Mediators or moderators
(Continued from previous page)									
Avan 2010; n=1035; South Africa[35]	Postnatal	Not reported	Pitt depression; inventory	Not reported	Richman child behaviour scale	2 years	Postnatal depression was associated with child behavioural issues (β 0·35, p=0·015)	SES, ethnic origin, birthweight, gestational age, maternal age, and growth	Mediated by stunted growth (β 0·294, p=0·111)
Hanington 2012; n=8598; UK (ALSPAC)[36]	Postnatal	Not reported	EPDS	Not reported	Rutter revised preschool scales	4 years	Postnatal depression was associated with increased risk of conduct problems (OR 1·74 [95% CI 1·33–2·52]); and emotional problems (OR 1·75 [1·36–2·52])	Maternal education, paternal depression	Mediated by marital conflict
Kersten-Alvarez 2012; n=142 (29 with depression); Netherlands[27]	Postnatal	Clinical interviews; DSM-IV	BDI	Not reported	Teacher report social competence; CBCL	Early school (child average age of 5 years)	Girls of mothers with postnatal depression showed less externalising difficulties than did controls	Child age and sex, maternal education, partner conflict, stressful life event, and father absence	Moderated by sex of the child; associations were stronger for girls than for boys
Letourneau 2013; n=10 033; Canada (NLSCY)[37]	Postnatal	Not reported	CES-D	Not reported	Physical aggression, inattention; NLSCY items	4–5 years	Postnatal depression was associated with inattention (OR 1·53, p<0·05) and physical aggression (OR 2·94, p<0·05)	SES, income adequacy, mothers' years of education, family structure, and family function	Effects for inattention mediated by later depression, parenting style, and family function
Fihrer 2009; n=75; Australia[38]	Postnatal	CIDI	CES-D	ADIS-P	Parent and teacher reports; CBCL; maternal repots mainly used	6–8 years	Postnatal depression was associated with child scores for internalising (β 0·35 [standardised estimate 0·11]) and externalising (β 0·25 [standardised estimate 0·12]) difficulties	Maternal education, non-English speaking	Associations mediated by later maternal depression, with evidence for significant indirect effects by use of path analysis

BDI=Beck depression inventory. CBCL=child behaviour checklist (internalising and externalising symptoms). BSI=brief symptom inventory (psychological symptoms). EPDS=Edinburgh postnatal depression scale. SDQ=strengths and difficulties questionnaire (internalising and externalising symptoms). ALSPAC=Avon longitudinal study of parents and children (UK). DAWBA=development and well being assessment. SES=socioeconomic status. YSR=youth self report (mental health). YSF=youth self report form. ICD=international classification of diseases. CIS=the clinical interview schedule. DSM=diagnostic and statistical manual. ITSEA=infant toddler social emotional assessment. CES-D=centre for epidemiologic studies depression scale. ADHD=attention deficit hyperactivity disorder. LMIC=low-income and middle-income countries. NLSCY=national longitudinal survey of children and youth (Canada). CIDI=composite international diagnostic interview. ADIS-P=anxiety disorders interview schedule for DMS-IV-parent version.

Table 2: Behavioural outcomes

depression. Depression and anxiety are substantially comorbid, and thus associations attributed to one, might include causes associated with the other. Several studies showed self-reported symptoms of antenatal anxiety are associated with internalising symptoms in childhood[14–17] and adolescence.[60] After symptoms of anxiety for both antenatally and postnatally were accounted for, no independent effect of antenatal depression occurred.[17]

A systematic review[61] reported associations between postnatal symptoms of anxiety and child emotional difficulties. Comparisons between depression and anxiety disorders in a few studies were assessed by diagnostic interviews; some specificity was noted in the nature of the early effects of anxiety disorders on infant distress to novelty (which is linked to behavioural inhibition),[22] but impairment in fear regulation was restricted to infants of mothers with depression.[24] Infants of mothers with post-traumatic stress disorder have an increased risk of difficulties in emotional regulation even after adjustment for symptoms of depression.[23]

Although research for other disorders is scarce, one report[62] shows that children of mothers admitted to mother and baby units with severe postnatal disorders are at an increased risk of a psychiatric (mainly emotional) disorder in adulthood compared with siblings who were not exposed to a postnatal episode.[62]

Behavioural (externalising) difficulties

Externalising difficulties include attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder, or symptoms of any of these.

Several studies have reported associations between antenatal depression and a child's externalising behaviour,[15,17,20,32] including when a child is adopted.[31] A small study[33] reported an association between antenatal depressive disorder and

	Time of first exposure	Exposure measure (maternal)		Outcome measure (child)	Age of children at follow-up	Results	Strengths and limitations	
		Clinical Interview or objective assessment	Self-report				Confounding variables included	Mediators or moderators
Hayes 2013; n=79; USA[39]	Antenatal	Diagnostic interview DSM-IV, SCID-IV	BDI-II	Strange situation*	12 months	Antenatal depression was associated with disorganised attachment (β 0·21 [SE 0·09], p<0·05; OR 1·23)	Sex of infant; parenting; antenatal antidepressant drugs	Parenting warmth and sensitivity at child age of 3 months reduced the association
Tharner 2012; n=627; Netherlands (generation-R)[40]	Antenatal, postnatal	Diagnostic interview DSM-IV, CIDI (postnatally)	BSI (antenatal, postnatal) EPDS (postnatal)	Strange situation*	14 months	Attachment insecurity was not associated with antenatal depression (BSI, Z score; OR 0·96 [95% CI 0·81–1·14]) and postnatal depression (BSI, Z score; OR 0·91 [0·75–1·10])	Maternal age, parity, maternal education, marital status, sex of child, gestational age at birth and at assessment, paternal psychopathology	Not reported
Tomlinson 2005; n=147 (98 on 18 month follow-up); South Africa[41]	Postnatal	Diagnostic interview DSM-IV, SCID-IV	Not reported	Strange situation*	18 months	Postnatal depression was associated with insecure attachment style (OR 2·98 [95% CI 1·26–7·01])	Partner support considered but not included in final model	Some evidence for mediation by maternal sensitivity or parenting at child age of 2 months
Murray 2011; n=100; UK[30]	Postnatal	Structured clinical interview for DSM-IV	Not reported	Strange situation*	18 months	Postnatal depression was associated with insecure attachment (OR 5·37 [95% CI 2·16–13·33])	Sex of infant, family adversity	Not reported

DSM=diagnostic and statistical manual. SCID=structured clinical interview for DSM-IV. BDI=Beck depression inventory. CIDI=composite international diagnostic interview. BSI=brief symptom inventory. EPDS=Edinburgh postnatal depression scale. *An observed experimental procedure where an infant's reactions to separation and reunion with their mother are used to categorise so-called security of mother-infant attachment.

Table 3: Attachment outcomes

antisocial behaviour in adolescence that was independent of postnatal depression. Several large longitudinal studies, including from LMICs, provided supportive evidence that symptoms and disorders of postnatal depression are associated with a child's externalising behaviour, particularly symptoms of attention deficit hyperactivity disorder, up to age 16 years.[20,34–38] In a large study of antenatal and postnatal maternal symptoms of depression, associations between antenatal symptoms and persistent childhood attention deficit hyperactivity disorder symptoms were diminished after postnatal symptoms were accounted for.[32]

Self-reported symptoms of maternal anxiety both antenatally[15,63] and postnatally[32] are associated with externalising disorders in childhood.[61] We found no studies that used clinical diagnostic interviews therefore associations between specific anxiety disorders and children's externalising difficulties remain to be established.

Few studies have investigated the effect of other perinatal psychopathology on behavioural outcomes. Results of a small study[26] suggested that infants of mothers with comorbid postnatal depression and personality disorder had reported dysregulated behaviour.

Attachment

Attachment is when a young child uses a caregiver as a secure base from which to explore and, when necessary, as a haven of safety and source of comfort.[64] This attachment is based on early experiences with caregivers' extent of responsiveness with the child.

Antenatal depression is associated with disorganised attachment (a form of insecure attachment), independently of postnatal depression.[39] In two meta-analyses,[65,66] postnatal depression was associated with an increased risk of insecure (especially disorganised) mother–infant attachment. This association is low or non-significant in community samples in relation to clinical samples and when depression is measured by self-report, in relation to diagnostic interviews.[40,66]

In a small sample of mothers with severe psychopathology and admitted to hospital postnatally, infants of mothers with unipolar depression, but not manic disorders, were more likely to show insecure attachment at aged 12 months than were infants of mothers without a perinatal disorder.[67]

Cognitive development

Antenatal depression (both self-reported symptoms and the disorder) is associated with low levels of general cognitive development, including IQ scores in childhood. However, effect sizes are generally small[17,42,44] and not all studies showed a significant association.[43] Postnatal depression has shown consistent associations (including studies from LMICs[45–49]) with a range of cognitive outcomes in early childhood, including infant ability to learn, achievement of developmental milestones, and language and general cognitive development.[26,37,50,51] Persistence of postnatal depression seems to be of particular importance in relation to cognitive development (table 4).[49–51]

Studies of the longer term effects of postnatal depression on cognitive functioning have been inconsistent. Results from a large study[44] showed an association between symptoms of postnatal depression and very small decreases in IQ scores at age 8 years, which became non-significant after accounting for maternal depressive symptoms after the postnatal period. Another large study[37] reported no association between postnatal depression and low maths acheivement at age 11 years and a small UK study[53] showed an association between postnatal depressive disorder and academic achievement in adolescence.

Several studies have investigated perinatal depression and anxiety by use of self-reporting. Associations with poor child cognitive outcomes were specific to symptoms of depression; these included studies of antenatal[42] and postnatal[42,45] symptoms. Other studies[52] have reported that symptoms of antenatal anxiety, rather than depression, were associated with poor exam achievements at age 11 years. An association was reported between antenatal symptoms of anxiety and impaired executive function abilities.[68]

We found no studies that reported associations between other disorders in mothers during the perinatal period and their child's cognitive development.

Child physical growth and development

Evidence is emerging that poor perinatal maternal mental health, especially in women at a socioeconomic disadvantage, is linked to poor infant growth. Although some studies, especially those done in HICs, have not noted such associations or only in subgroups,[69–71] increasing data from populations living in LMICs suggests that perinatal depression is associated with underweight and stunting in infancy[35,72–74] with effects persisting up to school age of 5 years.[72,75] Children of mothers with chronic depression (multiple episodes) might be particularly at risk of stunting or being underweight in LMICs.[76,77] By contrast, a systematic review[78] of studies in HICs reported chronic depression after childbirth was associated with the child being overweight.[78] Postnatal depression in LMICs is associated with high rates of diarrhoeal diseases in children,[79] which could contribute to their poor growth. Of the few studies of other perinatal disorders, some evidence exists that children of mothers with eating disorders, mainly those with anorexia nervosa, are at increased risk of poor growth.[80]

Feeding, eating habits, and attitudes

Children of mothers who had an eating disorder during pregnancy or in post partum are susceptible to difficulties during infancy, such as mealtime conflict.[80] Two longitudinal studies[81,82] reported an increased risk for negative outcomes in children of mothers with postnatal eating psychopathology. One of these studies[81] reported increased mealtime conflict at 5 years of age,

and concerns about body shape and weight and use of dietary restraint at 10 years of age. The second study showed that eating disturbance at age 5 years was predicted by many postnatal maternal variables, such as body dissatisfaction and the internalisation of the thin ideal[82] and at age 8 years, high postnatal maternal dietary restraint predicted high body dissatisfaction and dieting behaviours only in girls.[83]

Fathers

Traditionally, the mother's mental health received most attention. However, recognition of the importance of father's mental health is increasing.[84] Fathers can affect their children directly via quality of their interactions or genetic effects, or indirectly via their support to the mother and family environment. A large Norwegian population study[54] reported an association between symptoms of paternal antenatal depression and poor socioemotional and behavioural development of children at age 36 months;[54] postnatal symptoms were not assessed. However, another study[21] reported no evidence that paternal symptoms of antenatal depression were associated with child depression at age 18 years, rather only an association with paternal symptoms of depression postnatally.[21]

Symptoms of paternal postnatal mental disorders are associated with an increased risk of emotional and behavioural disorders for young children,[15,56] difficulties with their language development,[85] and depression at age 18 years.[21] Paternal and maternal depression in the postnatal period seem to have similar effects on behavioural outcomes, whereas maternal depression has a greater risk for emotional difficulties.[15,32,84,55] In a meta-analysis[86] of associations between both maternal and paternal disorders and their child's internalising or externalising difficulties across childhood, the younger the age of the child at the time of study, the greater the effect sizes for associations with maternal depression, but the reverse was reported for paternal depression.[86]

Mechanisms
Overview

The figure shows a model summarising possible mechanisms underlying the associations between parental psychiatric disorders and child outcomes. Biologically mediated effects of antenatal disorders (through in-utero effects) would be specific to mothers, whereas effects occurring postnatally and genetic effects might occur if either parent is affected by a disorder.

Genetic factors

Shared genetic risk factors probably account for part of the association between parental mental disorders at any time (including the perinatal period) and child susceptibilities. However, evidence exists for a substantial environmental contribution in the cause of mental disorders.[88] Correlations

	Time of first exposure	Exposure measure (maternal)		Outcome measure (child)		Age of child at follow-up	Results	Strengths and limitations	
		Clinical interview or objective assessment	Self-report	Objective assessment or interview	Questionnaire (parent or child reported)			Confounding variables included	Mediators or moderators
Koutra 2012; n=223; Greece (Rhea study)[42]	Antenatal	Not reported	STAI-Trait EPDS, personality trait (EPQ-R)	Bayley III	Not reported	18 months	Lower cognitive Bayley score was associated with antenatal depression (β –5·45 [95% CI –10·44 to –0·46]); and postnatal depression (β –5·80 [–11·65 to –0·05]); no effect of trait anxiety for cognitive development, no associations with maternal symptoms and Bayley language scores	Maternal age, maternal education, gestational age, quality of assessment, sex of child, and duration of breastfeeding, parent employment status	Personality traits associated with infant neuro-developmental scores
Tse 2010; n=1030; USA[43]	Antenatal	Not reported	EPDS	PPVT (language) WRAVMA (visual motor)	Not reported	3 years	No evidence for an association between antenatal depression and PPVT score (β –0·7 [95% CI –3·6 to 2·3]); WRAVMA (β –0·5 [–3·0 to 2·1])	Maternal race or ethnic origin, age, and education; parity, household income, pregnancy intention, partnership status, partner education, alcohol use and smoking, birthweight for gestational age	Not reported
Barker 2011; n=3298; UK (ALSPAC)[17]	Antenatal	Not reported	EPDS and Crown Crisp index	WISC (IQ)	Not reported	8 years	Low IQ was associated with antenatal depression (β –0·05, p<0·05), and postnatal depression (β –0·04, p<0·05); no association with anxiety	Adjusted for a cumulative risk score derived from SES, marital status, teenage mother, substance use and history of criminal activities, antenatal and postnatal anxiety and depression, mutually adjusted	Not reported
Evans 2012; n=6735; UK (ALSPAC)[44]	Antenatal	Not reported	EPDS	WISC (IQ)	Not reported	8 years	Antenatal depression was associated with a small decrease in IQ points, which attenuated after adjustments (β –0·64 [95% CI –1·68 to 0·40]); no association between postnatal depression independent of other time periods	Parity, maternal age smoking and drinking, parental social class, maternal education, disposable income, sex of child	Accumulation of depression in childhood best explained the association with low IQ points
Hadley 2008; n=431; rural Ethiopia[45]	Postnatal	Not reported	HSCL	Not reported	Denver II develop-mental test	3 months and 24 months	Maternal total symptoms were associated with low developmental scores (β –0·003 [SE 0·001], p<0·001); separating symptoms into depression and anxiety, depression (p<0·01) and not anxiety (p=0·51) was cause of the noted association	Child age and sex, stunted growth, maternal and paternal age, maternal and paternal body–mass indexes, household factors, paternal depression	Not reported
Galler 2000; n=226; Barbados[46]	Postnatal	Not reported	Zung scale*	Griffiths scale (DQ)	Not reported	6 months	Negative correlation between postnatal mood at age 7 weeks and total Griffiths score at age 6 months (r=–0·32, p<0·05)	Socioeconomic and home environment factors derived from Socioeconomic and Home Environment Questionnaire gestational age, parity, and birth order; infant weight at 3 months, length at 3 months and 6 months	Not reported
Patel 2003; n=171; India[47]	Postnatal	Not reported	EPDS	DASII (develop-mental assessment)	Not reported	6 months	Postnatal depression was associated with greater risk of poor development in infant (OR 3·3 [95% CI 1·2–8·8])	Birthweight and maternal education	Not reported
Hamadani 2012; n=488; Bangladesh[48]	Postnatal	Not reported	EPDS	Bayley (MDI) and reported milestones	Not reported	6 months and 12 months	Weak correlations between postnatal depression and impaired mental development (r=–0·04, p>0·05) and milestones (r=–0·08, p<0·05)	Child age at the time of assessment, socioeconomic factors, nutritional status, and postpartum maternal morbidity	Association attenuated once family care indicators were included

(Table 4 continues on next page)

	Time of first exposure	Exposure measure (maternal)		Outcome measure (child)		Age	Results	Strengths and limitations	
		Clinical interview or objective assessment	Self-report	Objective assessment or interview	Question-naire (parent or child reported)			Confounding variables included	Mediators or moderators
(Continued from previous page)									
Quevedo 2012; n=296; Brazil[49]	Postnatal	DSM-IV, MINI	Not reported	Bayley III language score	Not reported	12 months	Postnatal depression duration (depressed on no, one, or two occasions in first year) associated with lower language Bayley scores (β −2·87 [95% CI −5·01 to 0·64])	Maternal age, sex of child, parity, primary caregiver	Duration of exposure of postnatal depression associated with more impaired language
Kaplan 2011; n=134; USA[50]	Postnatal	Clinical interview, SCID, DSM-IV	BDI-II	Infant learning by observed conditioned attention task	Not reported	12 months	Infants aged 1 year of currently depressed mothers with relatively longer-duration depressive episodes (ie, perinatal onset) showed significantly poorer learning than infants aged 1 year of currently depressed mothers with relatively shorter duration depressive episodes (non-perinatal onset)	Not reported	Duration of perinatal episode exacerbated the association
Conroy 2012; n=200; UK[26]	Postnatal	Clinical interview, DSM-IV, SCID-I, NP	Not reported	Bayley II, MDI (mental subscale) ITSEA	Not reported	18 months	Postnatal depression was associated with impaired mental development (β −7·26 [95% CI −13·04 to −1·47], p<0·05)	Occupation, ethnic origin, partner status, later maternal depression, sex of infant, maternal sensitivity	Not reported
Sutter-Dallay 2011; n=598; France[51]	Postnatal	Clinical Interview DSM-IV-MINI	EPDS	Bayley II (MDI)	Not reported	2 years	Postnatal depression associated with a low Bayley MDI score (β −1·11 [95% CI −1·92 to −0·30], p<0·05)	Sex of child, maternal age, maternal education, income, parity	Mediated by later depression in mother
Kersten-Alvarez 2012; n=142 (29 with depression); Netherlands[27]	Postnatal	Clinical interviews; DSM-IV	BDI	PPVT-R	Teacher report social competence; CBCL	Early school (child average age of 5 years)	See table 1; postnatal depression was associated with low verbal intelligence only in girls	See table 1	Moderated by sex of the child; associations were stronger for girls than for boys
Letourneau 2013; n=10 033 (age 4–5 years), n=2427 (age 11 years); Canada[37]	Postnatal and later	Not reported	CES-D (12 items)	Language, maths achievement	Not reported	Between 4–5 and 11 years	Association between postnatal depression and low language at age 5 years (OR 1·39, p>0·05) and low maths achievement at age 11 years (OR 1·17, p>0·05)	SES, income adequacy, mothers' years of education, family structure, and family functioning	Mediated by later depression, family functioning and parenting style
Galler 2004; n=92; Barbados[52]	Postnatal	Not reported	Zung scale*	Exam scores at school entry (Eleven-Plus examination)	Not reported	11 years	Maternal anxiety (not depression) at 7 weeks correlated with overall exam score (r=−0·25, p<0·05)	Socioeconomic and home environment factors derived from Socioeconomic and Home Environment Questionnaire, gestational age, parity, and birth order	Not reported
Murray 2010; n=89; UK[53]	Postnatal	Clinical interviews SPI, SADS-L	Not reported	Bayley scales MDI at 18 months, McCarthy scale at age 5 years, WISC-III at age 8 years, GCSE exam results at the end of school age 16 years	Not reported	16 years	Postnatal depression associated with lower exam grade points (GCSEs) in children, particularly in boys whose mothers have postnatal depression than in boys whose mothers did not have postnatal depression	Maternal IQ and cognitive support, social class considered but not included in final model	Mediated by early cognitive impairments (on Bayley scale) and cognitive support from mother; effects limited to boys postnatal depression by interaction of the sex of the child (p=0·03)

STAI=state-trait anxiety inventory. EPDS=Edinburgh postnatal depression scale. EPQ-R=Eysenck personality questionnaire revised. PPVT=peabody picture vocabulary test. WRAVMA=wide range assessment of visual motor abilities. WISC=Wechsler intelligence scale for children. ALSPAC=Avon longitudinal study or parents and children (UK). SES=socioeconomic status. HSCL=Hopkins symptom checklist. DASII=developmental assessment scales for Indian infants. DQ=development quotient. MINI=mini-international neuropsychiatric interview. SCID=structured clinical interview for DSM-IV. DSM=diagnostic and statistical manual. BDI=Beck depression inventory. NP=non-patient edition. MDI=mental development index. ITSEA=infant toddler social emotional assessment. CES-D=centre for epidemiologic studies depression scale. SPI=standardised psychiatric interview. SADS-L=schedule for affective disorders and schizophrenia-lifetime. *Self report for anxiety and depression.

Table 4: Cognitive outcomes

(both passive and evocative) between genetic and environment factors[89] could account for a proportion of variance in associations between parental disorders and child outcomes through genetic-confounding. Our knowledge of this genetic contribution remains restricted.

Children's inherited genotype might also determine individual differences in their susceptibility to environmental effects. Interest has been shown in the possibility that gene polymorphisms can moderate the effect of many early-life adversities, including maternal mental disorders, on child development. Although some individual reports exist about effects of gene-by-environment interactions when applied to both antenatal[90] and postnatal environment,[91] results are often not replicated and the effect of single genetic

variations in modifying environmental exposures is likely to be very small and genetic susceptibility to environment will be defined by many, interactive variations in the genome.

Epigenetics

Epigenetic change (modification of gene expression, such as through methylation, without changing the genetic sequence) is a mechanism proposed to explain the long-lasting effects of early life experiences, including the perinatal environment, on biological and behavioural phenotypes.

Investigations have mainly been derived from animal studies; however, preliminary human studies report that antenatal stress and anxiety increases glucocorticoid

	Time of first exposure	Exposure measure (paternal)	Outcome measure (child)		Age of children at follow up	Results	Strengths and limitations	
		Self-report	Objective assessment or interview	Questionnaire (parent or child reported)			Confounding variables included	Mediators or moderators
Kvalevaag 2013; n=31 663; Norway (MoBa study)[54]	Antenatal	SCL-5	Not reported	SDQ, ITSEA, CBCL (operationalised into three summary scores: behavioural difficulties, emotional difficulties, and social functioning)	3 years	Paternal antenatal depression was associated with emotional problems (OR 1·45 [95% CI 1·19–1·77]); behavioural problems (OR 0·13 [0·11–1·40]); and impaired social functioning (OR 1·30 [1·06–1·59])	Paternal age, education, marital status, somatic conditions, lifestyle variables, use of alcohol, cigarette smoking, physical activity	Not reported
Velders 2011; n=2698; Netherlands (generation-R)[15]	Antenatal	BSI	Not reported	CBCL (internalising problem binary)	3 years	Antenatal paternal depression was associated with internalising (OR 1·15 [95% CI 1·05–1·26]) and externalising (OR 1·12 [1·02–1·23])	Maternal symptoms; see table 1	Mediated by parental hostility and prenatal family functioning
Pearson 2013; n=2475; UK (ALSPAC)[21]	Antenatal	EPDS	CIS-R	Not reported	18 years	Antenatal paternal depression was not associated with offspring depression (OR 0·9 [95% CI 0·7–1·1]); postnatal depression was associated with offspring depression in fathers with low education (OR 1·5 [1·1–2·0]) but not high education (OR 1·0 [0·7–1·3])	None (secondary analysis only)	Postnatal but not antenatal paternal depression was moderated by paternal education
Fletcher 2011; n=2620, Australia[55]	Postnatal	K6	Not reported	SDQ (binary)	4–5 years	Paternal postnatal depression was associated with behavioural problems (OR 1·93 [95% CI 1·75–2·14]); and low development and wellbeing (OR 1·65 [1·48–1·85])	Socioeconomic position, maternal education, and maternal depression	Paternal postnatal depression measured at child age of 2–3 years was more strongly associated with hyperactivity and pro-social in boys than with girls, and more strongly associated with emotional, conduct, and overall problems in girls than in boys
Ramchandani 2008; n=10 975; UK (ALSPAC)[56]	Postnatal	EPDS	DAWBA, DSM-IV	Not reported	6 years and 7 years	Paternal postnatal depression was associated with any disorder (OR 1·72 [95% CI 1·07–2·77]), behaviour or oppositional defiant disorder (OR 1·94 [1·04–3·61])	Maternal depression, paternal education, later paternal depression	Effects of paternal postnatal depression on hyperactivity, and emotional and behavioural problems were both stronger in boys than in girls

SCL=symptom checklist. SDQ=strengths and difficulties questionnaire (internalising and externalising symptoms). ITSEA=infant toddler social emotional assessment. CBCL=child behaviour checklist (internalising and externalising symptoms). OR=odds ratio. MoBa=Norwegian mother and child study. EPDS=Edinburgh postnatal depression scale. CIS-R=child interview schedule-revised. ALSPAC=Avon longitudinal study of parents and children (UK). BSI=brief symptom inventory (psychological symptoms). DAWBA=development and well being assessment. DSM=diagnostic and statistical manual.

Table 5: Outcomes for fathers

receptor (involved in stress responses) methylation (ie, silencing) in children.[92] Postnatally, maternal mental disorders might change maternal caregiving, which in animal studies lead to epigenetic changes in offspring.[93] Thus, epigenetic pathways might mediate the association between maternal disorders and child outcomes, although this hypothesis has not been formally tested.

Timing of perinatal mental health problems

Mental disorders or symptoms in pregnancy often continue after birth, thus raising questions about the contribution of antenatal and postnatal exposure and the extent to which their contributions are distinct, interactive, or cumulative. In particular whether antenatal effects are due to the direct effect on fetal development or because antenatal symptoms continue postnatally.

Mediating and moderating factors

Overview

A mediator is part of the causal pathway whereas moderators change the strength of association between exposure and outcome, which is sometimes referred to as effect modification.[87] Some factors can act as either mediators or moderators.

Fetal programming

Animal studies provide evidence that antenatal stress leads to maladaptive cognitive and behavioural changes in rodent offspring.[94] Often these changes are attributed to the effect of increased cortisol concentrations or other biological results due to stress on the offspring's brain development in utero.[94] However, findings of positive associations are inconsistent in human beings between antenatal depression or anxiety and increased cortisol concentrations,[16] implicating a more complex mechanism. For example, anxiety in pregnancy has been associated with the downregulation of the enzyme that metabolises cortisol and protects the baby in utero from excessive cortisol concentrations.[94] Thus, decreased expression of this enzyme might be a mechanism by which antenatal anxiety affects the fetus, even in the presence of normal concentrations of maternal cortisol. Importantly, although the present model is based on adverse effects of antenatal stress, clinical data suggests the possibility of a non-linear association between antenatal depression and fetal stress.[95] This postulation is consistent with some animal models, which indicates that some exposure to stress might be advantageous, with levels at both extremes leading to more negative fetal responses.[96]

Maternal programming

Mental disorders during pregnancy might disrupt neurocognitive changes in the mother that prepare women to respond towards their infants, known as maternal-programming.[97] Antenatal depression is associated with reduced maternal responsiveness towards infants independently of postnatal depression.[97] In rodents, antenatal stress reduces nurturing behaviour of maternal care.[98] This disruption to maternal programming might account for evidence that antenatal depression is associated with insecure attachment styles independently of postnatal depression[39] and an increased risk of children being exposed to maltreatment.[99]

Chronic exposure

Several studies have shown that effects of perinatal mental disorders are mediated by continued or recurrent exposure to the disorder during the child's life (tables 1–5).[29,37,44,51] That is, some variance in the association between perinatal disorder and child outcomes results from the persistence of the parent's disorder.

Interparent conflict

Perinatal mental disorders are associated with an increased risk of interparent conflict, relationship breakdown, and domestic violence[100] which, in turn, negatively affects children.[101] Evidence shows that interparent and family conflict mediates the association between symptoms of postnatal depression and child externalising behaviours.[36]

Parenting

A body of evidence suggests that the most important potential mediator is the quality of parenting. Data for each component of this mediating pathway shows first, perinatal disorders and symptoms can compromise the quality of parenting; second, compromised early parenting is associated with disturbances in child development; and third, disrupted parenting mediates the association between perinatal mental health and child outcomes.

Symptoms of mental disorders can affect a person's ability to respond to their environment, and thereby their parenting capabilities. For example, rumination and mood disturbance make it difficult for parents to focus their attention on, and provide contingent responsiveness towards, their infant's cues.[102] Several aspects of parenting are associated with postnatal disorders, including disengagement and withdrawal; missing of infant cues; poor responsiveness and particularly insufficient contingent responsiveness; intrusiveness;[58,103] and difficulty in thinking about and appreciating their children's perspectives, thoughts, and feelings.[103] Often, the term "lack of sensitivity" is used to incorporate these sometimes overlapping parenting capacities.[103] Most of this research has included maternal depression, but some evidence shows that different disorders are associated with specific disruption to maternal parenting. Mothers with eating disorders are more likely to use over-controlling and intrusive parenting, especially during mealtimes[80] and anxious mothers use more intrusive parenting[24] than do mothers without a psychiatric disorder. Mothers admitted to psychiatric mother and baby units (particularly those with either schizophrenia

and personality disorder) often display practical difficulties in baby care, poor emotional responsiveness, and intrusive behaviour with their infants.[67,104,105]

Parental difficulties in focusing their attention to infant signals and poor contingent responsiveness have been negatively associated with development of children's attention and cognitive functioning in studies with mothers with depression.[103] An infant's ability to control attention and thus effectively process information is, in turn, predictive of intellectual abilities.[106,107]

An important task for a parent is to support their infant when distressed, to maintain or recover their emotional equilibrium. Insufficient parental warmth, difficulties in regulation of an infant distress (so-called emotional scaffolding), and intrusiveness during stressful situations are negatively associated with child emotional regulation and behaviour.[103]

Two aspects of parenting are associated with a child's attachment security. First, disruptions to parental availability and appropriate responsiveness to attachment cues[108] and second, the parent's capacity to treat their child as a psychological agent with thoughts, feelings, and intentions.[109]

Disorder specific behaviours, such as speech and affect, manifested by a parent can be modelled by or transmitted to the child, leading to outcomes in the child that resemble the parent's disorder. Infants of mothers with depression are more likely to show sad affect and vocalise less, although these behaviours are probably in part due to infant distress as a result of the parent's insufficient appropriate responsiveness.[58,59] Infants of socially anxious mothers display similar responses to their mother, such as fear and avoidance of strangers.[110]

Observed parental sensitivity mediates the association between both antenatal and postnatal depressive disorders and attachment security,[39,41,111] and the association between postnatal depressive disorder and child emotion regulation during infancy[24] and depression at age 16 years.[30] Furthermore, parental responsiveness, cognitive support, and book reading to the child mediates the association between symptoms of postnatal depression and poor cognitive development.[37,53,112] Experimental evidence suggests that activation of negative cognitions, both in the context of postnatal anxiety and depressive disorders, diminishes the quality of parenting, which is associated with negative infant behaviour.[102]

Consistent with a role of modelling of disorder specific behaviours, mother and offspring depressogenic cognitions are correlated and partly mediate the association between perinatal maternal depression and the child's depression at age 18 years.[113]

Assumptions should not be made that the direction of effects is only from parent to child (figure). For example, some children are more difficult to raise because they frequently cry, sleep poorly, and are emotionally reactive. High irritability in young infants is strongly associated with the onset of maternal depression by 8 weeks' post
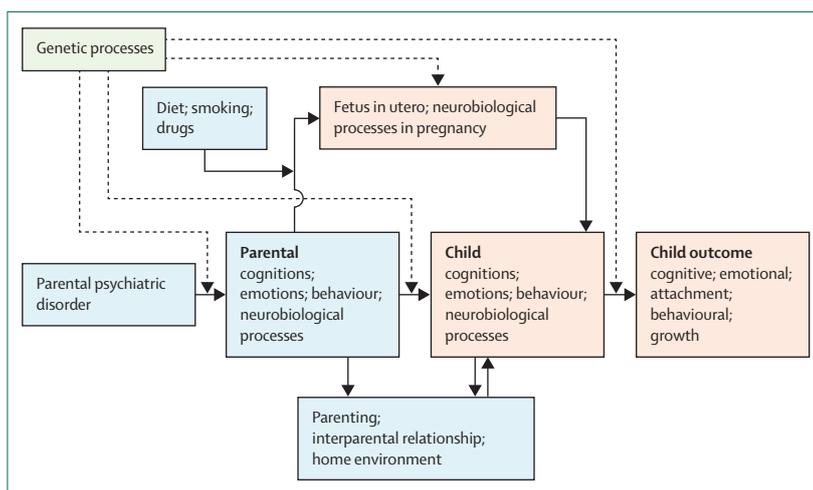

Figure: **Possible mechanisms underlying the association of parental psychiatric disorders and child outcomes**
Dotted lines show genetic processes. Solid lines show interactions. Orange colours refer to the child. Blue colours refer to the parents. Green represents genetic processes. Figure is based on figure 1 from Stein and Harold.[87]

partum.[114] These infant characteristics might evoke mood changes in carers, potentially setting a cycle of bidirectional effects between mother and child.

Moderating factors

Moderation can occur at two levels: a variable can moderate the primary association—eg, sex of the child can directly modify associations between postnatal depression and child behaviour—or can occur at the level of the mediator. For example, the association between perinatal disorders and parenting (the mediator) is often moderated by socioeconomic circumstances.

Important potential moderators of associations between perinatal disorders and child outcomes relate to the mother's practical and financial support and socioeconomic status.[115] Children whose mothers have the same extent of postnatal depression, but who are from a higher socioeconomic status, are less likely to be adversely affected. For example, in a large longitudinal study,[21] maternal education moderated the association between symptoms of postnatal depression and offspring depression at age 18 years. Only children of mothers with a low level of education showed an increased risk of depression themselves.[21] In a large community study,[112] socioeconomic status moderated the association between postnatal depression and language development. Quality of parenting was also measured in this study, showing that the moderating effect occurred at the level of parenting.[112] Evidence shows that a high socioeconomic status is protective of parenting in postnatal schizophrenia.[116] Social and emotional support, including partner support, reduces associations between postnatal depression and early cognitive development.[117]

In LMIC settings, the quality of parenting might have a greater role in a child's physical wellbeing, because the environment is harsher in LMICs than in HICs. Poverty,

overcrowding, and poor sanitation are common, and with suboptimum maternal care, these factors potentially increase the risk to physical health of children.

Many additional factors accentuate the risk of poor outcomes in children of parents with perinatal disorders: single parenthood, teenage parenthood (in HICs), and family disharmony.[57] The severity and duration of the disorder and particularly persistence after the postnatal period has consistently been shown to be an important moderator.[49,116,118] Results of a moderating effect of sex are inconsistent although girls have been suggested to be more susceptible to emotional outcomes[57] and boys to poorer behavioural and cognitive outcomes.[119] Children who have specific temperaments, those who show high levels of negative emotions, are more affected by the quality of maternal care and might also be more amenable to interventions to help them.[120]

Treatment and prevention

Although promising findings are emerging for the treatment and prevention of mental disorders during the perinatal period, few have investigated the potential benefit of such interventions for the wellbeing of the children.[3] The extent to which children benefit from such interventions is important. For example, although reliable evidence shows that maternal depression can be successfully prevented and treated,[121,122] amelioration of depressive symptoms alone has not been shown to improve mother–child interactions.[123] Thus, in addition to provision of treatment for depression, efforts need to directly target improving mother–child interaction to potentially improve child outcome, in view of evidence for the mediating role of parenting. That is, ongoing stressors, poor parenting, or persistent parental symptoms might contribute to difficulties for children even in the absence of the mother's disorder.

The few studies examining associations between treatment of maternal perinatal disorders and infant outcomes have reported the following findings. Mothers with postnatal depression who participated in psychotherapy (either non-directive supportive counselling, cognitive behavioural therapy, or psychodynamic psychotherapy) were associated with fewer toddler behavioural problems when aged 18 months than children of mothers assigned to routine care. However, no effect on cognitive development or attachment was noted.[124] Mothers' reduced levels of depression after 12 weeks of antidepressant drugs were associated with improvements in the quality of mother–infant interaction and infant play.[125] Interpersonal therapy for mothers with postnatal depression decreased their level of depression, but was not associated with significant improvements in parenting or child outcomes.[126,127] Finally, pregnant women with both diabetes and depression who participated in cognitive behavioural therapy had 6-month-old infants with better child development in psychomotor and behavioural functioning than did infants of mothers assigned to supportive counselling. Furthermore, improvements in depression symptoms in mothers treated with cognitive behavioural therapy correlated with infants' developmental outcomes.[128] Additional studies have also reported that antidepressant treatment in pregnancy might be associated with better infant developmental outcomes.[3,128] Overall, this understudied question of associations has yielded a mixed pattern of results suggesting additional investigations are needed.

Parenting interventions

Interventions designed to provide parent education and improve parent–infant interactions for women with perinatal disorders have had some promising findings. Most interventions focused on postnatal depression, with no reported studies on interventions delivered prophylactically in pregnancy. Home-visiting programmes improve the quality of maternal–infant interactions in women with depression.[129,130] Additionally, psychotherapeutic approaches for mothers who have depression, including a mother–infant psychotherapy group and interpersonal therapy, increases mother interactions with their infants compared with interactions of mothers with their infants in a wait-list control group.[131] A meta-analysis[132] concluded that the most effective parenting interventions for mothers with depression included infant massage, support groups, or interventions with more than one component.

Additional approaches have targeted mother–child interactions, often by use of individualised video-feedback which focused on improving the mothers' sensitivity to infant cues. In women with depression, video-feedback interventions have been associated with improvements in quality of interactions, infants' attachment security, and social competence compared with women who received little telephone parenting support.[133] Video-feedback treatment provided to mothers with eating disorders led to improvements in mother–infant interactions and increased infant autonomy by comparison with women who received supportive counselling.[134] An intensive (about once a week for 1 year) mother–toddler intervention for mothers of 20-month-old toddlers, who had had at least one major depressive episode since their child's birth, was associated with improved cognitive development and secure attachment when compared with mothers who had not had depression since birth.[135,136]

In women with schizophrenia, approaches focusing on increasing maternal sensitivity are effective in improving mother–infant interactions.[137] An assessment of video-feedback for mothers with acute postpartum psychiatric illness and their infants admitted to a mother and baby unit, reported improvements in mother–child interactions compared with mothers with psychiatric diagnoses living in the community who had not received inpatient care or video-feedback.[138]

Several randomised controlled trials in LMICs showed that psychological interventions delivered by local community health workers can have a positive effect on parenting and aspects of child development. A study in Pakistan[139] used a form of cognitive behavioural therapy together with parenting support that began during pregnancy.[139] Rates of postnatal depression were reduced, but no effect was noted on child growth, the principal outcome. Parents reported a reduction in rates of children's diarrhoea, increased rates of immunisation, and increased play with children, although the quality of parent–child interaction was not measured.[139] In a socioeconomically disadvantaged South African community, although not exclusively in the context of maternal depression, an intervention focused on helping mothers to attend to the details of the infant's communication and to respond sensitively.[111] This intervention led to improvements in the quality of mother–child interaction and increased rates of secure attachment.[111] In Jamaica, an intervention targeting child rearing and parenting self-esteem led to improvements in both maternal depressive symptoms and infant global development compared with intervention of standard care.[140] Determination of whether any improvements in mother and infant outcomes are sustained is an important question for future research.

Interventions involving fathers

Preliminary evidence shows that psychological interventions, such as cognitive behavioural therapy, can be effective in reducing symptoms of depression in fathers during the postnatal period.[141] However, no trials have assessed the effect of these interventions on parenting or child outcomes. Rather than focusing on treatment of maternal or paternal mental health in isolation, another approach is to move towards more inclusive perinatal mental health care, whereby the wellbeing of both parents are regarded and fathers are routinely involved.[141] In view of the importance of the interparental relationship, correlations between maternal and paternal symptoms, and evidence that paternal involvement can buffer the effect of maternal disorder on the child,[142] this inclusive approach could improve outcomes for the whole family. A preliminary assessment suggested that father inclusive information about perinatal mental health, provided by health-care systems, improved paternal response to the newborn baby.[141]

Policy implications and conclusions

From a policy perspective, an essential first step is to identify both parents and children who are at an increased risk of adverse outcomes as a result of perinatal mental disorders to enable early treatment and prevention. Children also have needs that are not necessarily met by treating the parental disorder alone. Although much progress has been made to understand the mechanisms and pathways to both healthy and disturbed development of children, much remains to be done. Understanding of mechanisms, especially modifiable pathways, is key to development of interventions and identification of at risk groups. For example, the quality of parenting is important and an understanding of the relationship between specific parenting behaviours and different child outcomes is crucial. Furthermore, if researchers can clarify the process that environmental factors, such as education and social support, mitigate the effects of perinatal disorders on the child, this knowledge could be used in prevention. Development of evidence-based interventions and preventive strategies for these parents and children, including routine involvement of the father, is urgently needed. In view of increasing evidence that experiences in the early years of life are crucial for healthy development and productivity later in life and the number of people affected,[3] interventions and prevention strategies should be a public health priority. Recognition is needed that addressing perinatal mental disorders can contribute substantially to the Millennium Development Goals and the post-2015 Millennium Development Goals agenda, specifically those related to child nutrition and early development, education, and maternal health (including antenatal care).[143]

Although an association exists between children whose parents have mental disorders during the perinatal period and an increased risk of a range of adverse child outcomes, such negative outcomes are not inevitable. Most effect sizes for associations between disorders in parents and outcomes in children were moderate or small. Moreover, we identified evidence for moderation whereby factors, such as low socioeconomic status, absence of social support (including partner support), and persistence of the parental disorder, increased the child's risk of adverse outcomes. Conversely, when disorders occur in the absence of social adversity and if they are of short duration, the risks to the child are generally low. Children in socioeconomically disadvantaged circumstances, especially in LMICs, are more likely to be both exposed to parental disorders and if their parent has a disorder to be affected than in children whose parents do not have a disorder, highlighting the need for global strategies that focus on integration of perinatal mental health and public health. Nonetheless, despite adversity many children in such situations develop normally and remain healthy, showing resilience of parental care and child development.

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