**Malnutrition and depression in pregnancy and associations with child behaviour and cognitive function: a review of recent evidence on unique and joint effects.**Laura S. Bleker1-2, Susanne R. de Rooij2, and Tessa J. Roseboom1-2

*1Amsterdam UMC, location Academic Medical Centre, Department of Obstetrics and Gynecology, Amsterdam, The Netherlands  
2Amsterdam UMC, location Academic Medical Centre, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

Address correspondence to Laura Bleker, MD, Amsterdam UMC, location Academic Medical Centre, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. Email: [l.s.bleker@amc.uva.nl](mailto:l.s.bleker@amc.uva.nl)

**Abstract**

**Background and aim:** Accumulating studies suggest that prenatal experiences can shape children’s neurodevelopment. Malnutrition and depression occur in pregnancy relatively often and may affect child neurodevelopment independently as well as synergistically. We aimed to provide an overview of recent studies that have examined malnutrition and/or depression in pregnancy and associations with children’s behavioural problems and cognitive function.

**Methods:** We conducted a literature search in Pubmed, using the main search terms: ‘depression’, ‘nutrition’, ‘BMI’, ‘pregnancy’, ‘offspring’, ‘cognition’, and ‘behaviour’. We included studies in human populations published from 2013 onwards.

**Results:** The literature search yielded 1531 articles, of which 55 were included in the current review. We presented the evidence on the associations between prenatal markers of nutritional status and/or depression and child behaviour and/or cognitive function. We additionally discussed interventions and mechanisms.

**Conclusion:** Bothmalnutrition depression in pregnancy are associated with increased externalizing behavioural problems and attentional deficits, and to some extent with poorer cognitive function in the children, but the evidence is not conclusive. Studies on synergistic effects of both factors on child behaviour and cognitive function are still scarce, and more research is needed. Potential shared mechanisms include the hypothalamic pituitary adrenal axis, the immune system, epigenetics, and oxidative stress.

**Keywords:** Prenatal programming; malnutrition; depression; pregnancy; cognition; behaviour; mechanisms

**Introduction**

The fetal brain is plastic – it is able to adapt to its environment. This neurodevelopmental plasticity allows for learning and shaping of the brain, and acts by adjusting physiological processes to meet external demands. These adaptations are partly driven by environmental cues, which are able to alter the ‘set-point’ of several physiological brain processes that are, to some extent, irreversible (Gluckman and Hanson 2004; Swanson and Wadhwa 2008). Therefore, environmental stressors during the fetal stage can have profound consequences for neurodevelopment, potentially leading to increased vulnerability to chronic (mental) health problems in later life. Maternal malnutrition and depression in pregnancy are both profound and common stressors that can negatively affect child neurodevelopment and subsequent later life health (Roseboom et al. 2011; Van den Bergh et al. 2017). Both undernutrition and obesity can reflect a state of (relative) malnourishment, and a recent report of Unicef concluded that 1 out of 3 people in the world are affected by either one of the two (2017). Depression is a frequently occurring disorder during pregnancy, with prevalence rates of 7.4%, 12.8% and 12.0% for the first, second, and third trimester, respectively (Bennett et al. 2004). In developing countries, the prevalence is even higher, with a pooled prevalence estimate of 25.3% for depression occurring during pregnancy, prior to childbirth, and 19.6% for postpartum depression (Gelaye et al. 2016). Conflicts and poverty in low to middle-income countries contribute to this high prevalence of depression (Bogic et al. 2015; Chung et al. 2016). Moreover, malnutrition and depression in pregnancy can exist alongside and affect each other, thereby adding on to the negative impacts that both phenomena independently may have on fetal neurodevelopment (Monk et al. 2013). Although different biochemical and physiological changes in both the maternal and fetal compartment may underlie the associations between malnutrition and/or depression in pregnancy and altered child neurodevelopmental outcomes, they are likely to partly overlap and influence one another as well. Therefore, both factors need to be studied in the context of the other, to determine the relative and/or synergistic impact on developmental trajectories (Monk et al. 2013). In this review, we sought to evaluate studies that have been published in the past 5 years on malnutrition and/or depression in pregnancy on neurodevelopmental outcomes in children, with a particular focus on identifying studies that have addressed both exposures simultaneously. We additionally searched for studies that assessed effects of interventions. Because of the broad scope of this review and the abundance of studies that include various aspects of neurodevelopment in children in association with maternal depression and/or markers of nutritional status in pregnancy, we decided to limit our selection in terms of the outcome, selecting only studies that assessed behaviour and/or cognitive function in children.

**Literature Search**

An electronic literature search was performed in PubMed. The search was performed on September 10, 2018. We used standard vocabulary terms (e.g. MeSH and text words) for searching title and abstract, and Boolean operators. We included the following terms, as well as synonyms, in our search; ‘depression’, ‘nutrition’, ‘BMI’, ‘pregnancy’, ‘offspring’, ‘cognition’, and ‘behaviour’. The inclusion criteria were: (1) original research papers published since 2013 that (2) related only to humans. Included studies needed to be (3) cohort studies including women during their pregnancy in which (4) depression symptoms were (self)reported, and/- or a marker of nutritional status was measured such as the type of diet, vitamin D status, (pre-pregnancy) BMI or obesity, or famine exposure. Study outcomes were either (5) child behaviour (e.g. total behavioural problems on the Child Behaviour Checklist (CBCL)) or (7) child cognitive function (e.g. full scale intelligence on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), or a cognitive component on a general developmental assessment such as the Bayley Scales of Infant Development (BSID-II)). The exclusion criteria were: (1) articles for which full text was not available, (2) conference abstracts, and (3) articles that were not written in the English, Dutch, German or French language. A total of 1531 records were identified. All records were exported to EndNote. After removal of duplicates (n = 81) and exclusion of studies that did not meet the inclusion criteria or that met any of the exclusion criteria (n = 1395), we selected 55 studies for inclusion in the current review.

We presented the findings from the included studies in separate paragraphs. In the first paragraph we described studies that have addressed both depression and a marker of nutritional status in pregnancy in relation to child behaviour and/or cognitive function, either through calculating an interaction term or by performing a path analysis. In the second paragraph we discussed studies that assessed malnutrition in pregnancy and examined associations with child behaviour and/or cognitive function. We divided this paragraph into subsections, according to the type of marker/exposure during pregnancy (type of diet, vitamin D, (pre)pregnancy BMI, or famine) and the last two subsections included intervention studies and a conclusion. The third paragraph included studies that measured depression symptoms in pregnancy and examined associations with child behaviour and/or cognitive function. This paragraph was divided into subsections according to the screening tool that was used to measure depression symptoms. Here, we also finished with subsections on intervention studies and a conclusion. The fourth paragraph included a concise description of proposed biological mechanisms that may link both maternal malnutrition as well as depression during pregnancy to altered behaviour and/or cognitive function of the child. The fifth and sixth paragraph comprised a general discussion and a final conclusion.

1. **Malnutrition, depression and child behaviour and cognition**

Our search yielded four studies that specifically aimed at assessing the associations between both malnutrition and depression in pregnancy with child behaviour and/or cognitive function (table 1). One study examined moderation effects of maternal depression and manganese levels (a nutrient that is essential for brain development, but which in high levels may be neurotoxic (Rodriguez-Barranco et al. 2013)) in maternal and cord blood, and found that both 3rd trimester manganese levels as well as depression symptoms were independently negatively associated with child cognitive function at the age of 24 months. Moreover, the authors observed a statistically significant interaction between manganese levels and depression symptoms, indicating that the association between higher manganese (in both maternal as well as cord blood) and lower child language scores was stronger among women with elevated depression symptoms (Munoz-Rocha et al. 2018). Three studies examined independent and inter-related associations of a marker of maternal nutritional status and depression in pregnancy with child behaviour and/or cognitive function by means of a path analysis. One study showed that higher prenatal maternal depression was prospectively associated with a more unhealthy diet, both during pregnancy as well as postnatal, which in turn was associated with more child emotional-behavioural dysregulation problems up to the age of 7 years. Both factors were also independently associated with higher child emotional-behavioural dysregulation after adjusting for multiple confounders including parity, poverty and maternal education (Pina-Camacho et al. 2015). Barker et al. reported similar results, showing that above and beyond postnatal depression, prenatal depression symptoms were related to more unhealthy diets of the pregnant women, which in turn were associated with reduced cognitive function of the children at the age of 8 years. Here also, both elevated depression symptoms and an unhealthy diet in pregnancy predicted poorer child cognitive function independently, as did postnatal diet (Barker et al. 2013). One final study examined behavioural problems in children of women with an eating disorder in pregnancy, and showed that children of women with Bulimia Nervosa in pregnancy were more likely to show hyperactivity (only in girls) and emotional and conduct disorders (only in boys), which was mediated by pregnancy anxiety and depression symptoms, although the number of women with an eating disorder was relatively small (Micali et al. 2014). In conclusion, seemingly few studies exist that have addressed both nutrition and depression in pregnancy and their joint association with child behavioural problems and/or cognitive function, with only one study formally testing for an interaction effect. In addition, evidence from three studies examining independent and interrelated associations between maternal nutrition and depression with child behavioural problems and cognitive function suggest that maternal depression symptoms and nutrition show important developmental associations, but are also independently associated with increased behavioural problems and poorer cognitive function in the children. These type of studies are important as they provide more insight into how maternal depression can lead to poor nutrition and vice versa, and how this may affect child neurodevelopment.

1. **Malnutrition in pregnancy and child behaviour and cognition**
   1. **Diet**

The diet of the mother during pregnancy may directly affect the nutritional environment of the fetus, which is likely to influence the development of many organs including the brain (Monk et al. 2013). A healthy diet is generally defined as a diet that is rich of nutrients, and restricted in salt, sugar and solid fats (WHO 2015). We identified three studies that examined the association between diet in pregnancy and child behaviour (table 2). Two studies distinguished a ‘healthy’ and an ‘unhealthy’ diet (Galera et al. 2018b; Jacka et al. 2013), whereas in one study the ‘Mediterranean diet’ (high loadings on vegetables, (shell)fish, vegetable oil, fruit, and eggs, low loadings on processed meat) was compared to a ‘Traditionally Dutch’ diet (high intakes of fresh and processed meat and potatoes, margarines and low intakes of soy and diet products) during pregnancy (Steenweg-de Graaff et al. 2014). All studies assessed child behaviour. One study, including over 23000 participants, showed that higher intakes of unhealthy foods during pregnancy predicted externalizing, but not internalizing behavioural problems among children, independently of other potential confounding factors including childhood diet (Jacka et al. 2013). In another study, both a low adherence to a Mediterranean diet as well as a high adherence to a Traditionally Dutch diet were positively associated with child externalizing behavioural problems, but again, not with internalizing behavioural problems (Steenweg-de Graaff et al. 2014). In line with these earlier studies, a recent study showed that a ‘low healthy diet’ in pregnancy as well as a ‘high Western diet’ was associated with children’s trajectories of high hyperactivity-inattention symptoms between the ages of 3 to 8 years (Galera et al. 2018a). In conclusion, higher adherence to a more unhealthy diet in pregnancy potentially poses a risk for increased externalizing behavioural problems of the child. This may be explained by the fact that fatty acids influence the development and maturation of neural structures, and the concentration of fatty acids in the fetus depends on maternal fatty acids, and thus, her dietary intake. In particular, the omega-3: omega-6 long-chain polyunsaturated fatty acids ratio is believed important for neural development, which is more evenly balanced in ‘healthy diets’ due to their richness in vegetable oils and lean fish (Hadders-Algra 2008). This was also shown in a large study in which associations between fatty acid status during pregnancy and child behavioural problems were examined. The authors reported that a higher omega-3: omega-6 ratio in pregnancy was associated with decreased odds of parent-reported as well as combined parent/teacher-reported emotional problems of the children (Steenweg-de Graaff et al. 2015).

* 1. **Vitamin D**

A healthy diet, as described in the previous section, may exert its positive effects on child neurodevelopment because of the high levels of long-chain omega 3 fatty acids that are present in, for example, oily fish. However, oily fish is also a great dietary source of Vitamin D which may also explain the improved child outcomes in children of mothers that adhered to a healthy diet in pregnancy compared to a less healthy diet. We identified five studies that examined the association between Vitamin D levels in pregnancy and child behaviour and cognitive function (table 2). One study showed that vitamin D-deficiency in pregnancy was associated with an increased risk for attentional problems in children aged 4 to 5 years (Morales et al. 2015). However, Strom et al. did not show an association between maternal vitamin D level in pregnancy and the prevalence of an ADHD diagnosis in children aged 22 years (Strom et al. 2014). The inconsistency in findings may be explained by the differences in child age at the assessment, or by the fact that Strom et al. defined ADHD as a first admission diagnosis or prescription of medication, whereas Morales et al. measured ADHD symptoms along a continuous scale. In terms of cognitive function, three out of four of the included studies showed no benefit of higher maternal Vitamin D-levels in improving child cognitive function (Darling et al. 2017; Strom et al. 2014; Veena et al. 2017). Only one study observed that higher vitamin D status in pregnancy was associated with better attention and executive functioning as shown by a faster reaction time (Brouwer-Brolsma et al. 2018). The difference in findings may be explained by the fact that Brouwer-Brolsma et al. assessed cognition at a younger age (5-6 years) compared to the other studies (22 years (Strom et al. 2014), 8-9 years (Darling et al. 2017), and 9-14 years (Veena et al. 2017)). The study results suggest a short-term beneficial effect of higher maternal Vitamin D status during pregnancy on improved child behaviour and cognitive function which does not persist into later childhood.

* 1. **(Pre-)Pregnancy BMI**

Obesity is considered a global epidemic, also affecting women in their reproductive phase (NCD-RisC 2017). During pregnancy, an obesity-induced inflammatory response may result in dysregulation of placental transport of excess nutrients or micronutrient deficiencies and increased oxidative stress in the intrauterine environment, which may negatively affect fetal neurodevelopment (Bolton and Bilbo 2014; Georgieff 2006). However, socioeconomic and family risk factors associated with obesity are likely to confound the associations between maternal obesity and offspring behaviour and cognitive function. We identified eight studies that examined (pre-) pregnancy BMI or obesity in pregnancy in association with child behaviour (table 2). One study reported a trend towards more aggressive behaviour and more externalizing behavioural problems in children of overweight women compared to children of normal weight women in pregnancy (Antoniou et al. 2014). A larger study also showed that children aged 6 years of women with obesity in pregnancy had increased odds of a wide range of adverse behaviours including more emotional symptoms, more attention-deficit/hyperactivity disorders (ADHD), and more speech language problems compared to children of normal weight women in pregnancy, also after adjustment for relevant confounders (Jo et al. 2015). Another study showed that pre-pregnancy overweight and obesity were associated with a significantly increased risk of presenting with an affective problem score on the CBCL Diagnosed and Statistical Manual of Mental Disorders (DSM)-Oriented Scales (Achenbach 2001) throughout childhood above the clinical cut-off for morbidity, compared to children of women with a healthy pre-pregnancy BMI, in fully adjusted models (Robinson et al. 2013). Finally, Mina et al showed increased hyperactivity, more sleep, conduct, and externalizing problems, and more anxious/depressed and aggressive behaviour in children at the age of 3 to 5 years born to obese women, which was also independent of demographic factors (Mina et al. 2017). One study assessed both child behaviour and cognitive function and showed that maternal obesity in pregnancy was associated with lower cognitive function and also with increased behavioural difficulties and more ADHD symptoms in children at the age of 4 years (Daraki et al. 2017). Three studies examined the association between pre-pregnancy BMI and child cognitive function, with conflicting results (table 2). One study showed that at the ages of 6, 10 and 14 years, offspring academic scores were inversely associated with maternal pre-pregnancy BMI beyond 22 kg/m3 (Pugh et al. 2016). Another study also showed that pre-pregnancy obesity was associated with reduced infant cognitive function at 11-22 months in both cohorts, also after adjusting for socioeconomic variables and paternal BMI (Casas et al. 2013). In contrast, although Bliddal et al. also observed that pre-pregnancy BMI was associated with lower child IQ at the age of 5 years in a large cohort, they reported a similar association between paternal BMI and child IQ, suggesting that the effect was not pregnancy-related (Bliddal et al. 2014). The conflicting findings may be explained by the fact that in the study sample from Pugh et al., the prevalence of maternal obesity was relatively high compared to the cohort studied by Bliddal et al., indicating larger power to detect smaller effects. Although the methodological designs of these studies cannot determine causality, the associations between higher (pre-) pregnancy BMI and obesity in pregnancy and mainly increased child behavioural problems were robust after accounting for various potential confounders, suggesting a direct independent pathway leading from obesity in pregnancy to adverse child neurodevelopmental outcomes. Possibly, socioeconomic status and family risk factors play a more important role in child cognitive development compared to emotional-behavioural development.

* 1. **Famine**

Studying the effects of undernutrition during pregnancy on child behaviour and cognitive function in humans is complicated, but important, given the increase in famine worldwide (2017). The Dutch Famine study (de Rooij et al. 2010; Roseboom et al. 2011) and the Chinese Famine study (Huang et al. 2013; Kang et al. 2017) are two examples of equivalents to an experimental set-up that have been used by many researchers to investigate the effects of prenatal undernutrition on various health parameters in humans. Although these studies have not provided the opportunity to examine the effects of prenatal undernutrition on behaviour or cognitive function in the exposed offspring during childhood, the effects in adulthood on cognitive function have been examined. In the past 5 years, one study was published in which cognitive function was assessed in adults who had been prenatally exposed to the Chinese famine, which lasted from the late 1950s to the early 1960s. Exposed individuals showed poorer visual-motor skills, mental flexibility, and selective attention in a cognitive task compared to a control group, indicating a long-lasting negative effect of maternal undernutrition during pregnancy on cognitive function (Li et al. 2015).

* 1. **Intervention studies**

Our search yielded five studies that examined whether maternal nutritional supplementation during pregnancy would improve child behaviour and/or cognitive performance (table 3). All trials were performed in developing countries, and examined the effects of a (micro)nutrient supplement during pregnancy on cognitive function of the children, during the first 2 years of life (Christian et al. 2016; Prado et al. 2016a; Prado et al. 2016b; Srinivasan et al. 2017) and at 12 years of age (Dulal et al. 2018), with sample sizes varying from 178 (Srinivasan et al. 2017) up to 1320 mother-child dyads (Prado et al. 2016a). Srinivasan et al. examined the effect of oral vitamin B12 supplementation in pregnancy on cognitive function in children at the age of 9 months, but failed to show a beneficial effect (Srinivasan et al. 2017). Prado et al examined the effect of a small-quantity lipid-based nutrient supplement during pregnancy in two study samples, one in Malawi and one in Ghana, on child language, socio-emotional and executive function at 1.5 years of age, and did not observe any beneficial effect either (Prado et al. 2016a; Prado et al. 2016b). Again, in a trial in Bangladesh, prenatal multiple micronutrient supplementation was not associated with cognitive function at 2 years of age, despite a decrease in stunting at birth and at 3 months of age (Christian et al. 2016). Finally, a study in Nepal also did not show any beneficial effect of prenatal micronutrient supplementation on child full-scale IQ or executive functioning at the age of 12 years (Dulal et al. 2018). We did not identify studies on the effects of supplementation of (micro) nutrients during pregnancy on child behaviour. In conclusion, there is little evidence to support the hypothesis that supplementation of (micro) nutrients during pregnancy improves child cognitive function. However, it is also possible that the diets from the pregnant women in the control groups provided sufficient (micro) nutrients for an appropriate cognitive development.

* 1. **Conclusion**

In conclusion, recent evidence has shown that an unhealthy/Western diet, a deficiency in specific (micro)nutrients such as vitamin D, as well as overweight/obesity in pregnancy are associated with increased child behavioural problems, in particular externalizing behavioural problems and attentional deficits. Associations with child cognitive function vary, depending on the exposure, showing more consistent associations when the exposure included prenatal famine (although cognitive function was only studied in adulthood) or maternal (pre-pregnancy) obesity, but showing less consistent associations with vitamin D status. Beneficial effects of various maternal nutritional supplements on child cognitive function have not been shown.

1. **Depression in pregnancy and child behaviour and cognition**

Depression is a common condition in pregnancy (Bennett et al. 2004), and can impair a woman’s self-care (Zuckerman et al. 1989). Moreover, children born from prenatally depressed women are at risk for low birth weight (Accortt et al. 2015), as well as a wide range of neurodevelopmental disorders in childhood and adolescence (Glover 2015; Van den Bergh et al. 2017). Potentially, through dysregulation (either over activation or desensitization) of the hypothalamic-pituitary-adrenal (HPA) axis, shifts in immune system function, increased oxidative stress or epigenetic alterations, the unborn child’s neurodevelopment may be affected, resulting in behavioural problems and cognitive deficits in childhood, as has been shown in animal studies (Kaiser and Sachser 2005). There is increasing evidence from human studies suggesting that depression during pregnancy, usually defined as reporting a score above a certain threshold on a screening questionnaire that indicates possible depression, is associated with increased child behavioural problems and poorer cognitive function. We listed recent evidence according to the screening tool that was used to assess depression symptoms during pregnancy in the women.

* 1. **Edinburgh (Postnatal) Depression Scale (E(P)DS)**

The Edinburgh (Postnatal) Depression Scale (E(P)DS) is a set of 10 screening questions that can indicate whether an individual has elevated symptoms of depression and anxiety during pregnancy and in the year following the birth of a child (Cox et al. 1996). We identified nine studies that used the EPDS as a screening tool and three studies that used the EPDS in combination with additional screening tools (table 4). Eleven studies assessed child behaviour (table 4). Park et al. identified three trajectories of depression symptoms from pregnancy to 3 years postpartum; stable low, decreasing or increasing. They reported increased internalizing and externalizing behavioural problems in children born to women with increasing depression symptoms throughout pregnancy at age 3, and poorer performance on a cognitive task at age 6 (Park et al. 2018). In contrast to their hypothesis, they found that children of women with decreasing symptoms over time (being high in pregnancy alone) performed better compared to children of women with stable low symptoms on a cognitive task at the age of 6. However, their sample was relatively small (n = 147) and the women in their sample reported overall low levels of depression. One study assessed a wide variety of behavioural symptoms in children aged 10 to 11 years born to women with prenatal depression, and after comprehensive adjustment for many psychological and socio-demographical factors, only the association with increased attentional problems, by teacher-report, remained (Leis et al. 2014). Likewise, in the ALSPAC cohort study, prenatal depression was associated with a higher risk of child attentional problems at the age of 5 to 6 years, also after adjustment for postnatal depression (Van Batenburg-Eddes et al. 2013). In contrast, a similar analysis in the Dutch Generation R cohort showed that although prenatal depression was associated with increased child attentional problems in 3-year-old children, this did not survive adjustment for postnatal mood (Van Batenburg-Eddes et al. 2013). The authors therefore suggested that the increased risk for child attentional problems after prenatal depression exposure may be largely explained by residual confounding, and only partially by prenatal exposure to increased maternal depression symptoms. Also, the timing of the exposure may have specific effects, depending on the outcome measured. For example, a study in Norway including 1235 women-child dyads reported increased social-emotional problems in 2-year old children exposed to higher levels of prenatal depression in adjusted analyses (Junge et al. 2017). However, another Norwegian study with a similar sample size could not replicate this finding in children aged 18 months when the postnatal period was taken into account (Fredriksen et al. 2018). These opposing findings are striking, considering their similarity in study settings and sample sizes. This may be explained by the fact that Fredriksen et al. measured depression symptoms at various time points in pregnancy, whereas Junge et al. only measured this once, in late pregnancy. Also, they used different instruments to assess child behaviour. This also emphasizes that, even in cohorts that are very similar, substantially different effects on behaviour and/or cognitive function may be observed according to the timing of the exposure in pregnancy as well as the tool by which the outcome is measured. This was also shown by Korhonen et al. In this study, elevated depression symptoms during pregnancy were positively associated with externalizing problem behaviour in children aged 16 years, whereas higher depression symptoms 2 months after birth were associated with more internalizing problems, increased maternal depression symptoms in early childhood showed an association with poorer child social competence, and concurrent elevated depression symptoms were associated with more externalizing problems (Korhonen et al. 2014). In line with the observations made by Park et al., it was not the severity of depression symptoms per se, but the congruity of depression symptoms in the pre-and postnatal period that predicted child behavioural outcomes. The differential effects of different trajectories of depression symptom severity across pregnancy on child behavioural outcomes has been shown in more studies. One study showed that prenatal depression significantly correlated with higher total as well as internalizing behavioural problems at age 2 in the children, but the effects were largest in children born to women reporting an increase in depression symptom severity across pregnancy, followed by women with a stable-moderate trajectory, compared to a stable-low symptoms pattern (Guyon-Harris et al. 2016). Another study demonstrated that children of women with moderate or persistent high symptoms of prenatal depression were at increased risk of emotional-behavioural difficulties at age 3, compared to women with no or few symptoms (Kingston et al. 2018). Similar observations were described in another study, showing that 4-year-old children born to women with either a trajectory of stable subclinical depression, increasing depression or persistently high depression through pregnancy were 2 times more likely to show emotional-behavioural difficulties compared to women with minimal symptoms (Giallo et al. 2015). One study examined the effects of positive maternal mood on child behaviour and cognitive function, by combining the EPDS with two other psychiatric screening tools (Beck Depression Inventory - Second Edition (BDI-II), and the State-Trait Anxiety Inventory (STAI)) to construct a positive maternal mood scale. They showed that a positive mood predicted better child cognitive function and less peer aggression at 12, 18 and 24 months, implying ‘a distinct beneficial effect of positive maternal mood on child neurodevelopment from the mere absence of depression and anxiety symptoms in pregnancy (Phua et al. 2017). Two studies examined the association between EPDS-score in pregnancy and cognitive function of the children (table 4), and both studies showed that high depression symptoms in pregnancy were associated with lower cognitive function in the children at 18 months (Koutra et al. 2013), and 8 years old (Jensen et al. 2014).

* 1. **Center for Epidemiological Studies - Depression (CES-D)**

Six studies used the Center for Epidemiological Studies Depression Scale (CES-D) to measure depression symptoms in pregnancy. The CES-D scale is a short self-report scale designed to measure depression symptomatology in the general population, but is also often used for screening for probable depression among pregnant women (Radloff 1977). Seven studies were identified that used the CES-D as a screening tool (table 4), of which six studies assessed child behaviour. Raskin et al reported increased behavioural problems at 24 months in children of women with elevated depression symptoms in pregnancy compared to children of women without symptoms, also after the results were adjusted for postnatal depression. In addition, children born to women with a steeper increase in symptoms over time exhibited more behavioural problems compared to women with a stable trajectory of symptoms (Raskin et al. 2016). Another study reported that increased depression symptoms in pregnancy alone were not independently associated with behavioural problems in the 5-year-old children. However, here again, the trajectory of symptoms across and after pregnancy seemed to impact the child’s behavioural phenotype, showing that children of women with persistent symptoms during and after pregnancy, either intermediate or high, exhibited the greatest levels of emotional and behavioural difficulties (van der Waerden et al. 2015). Another study showed that high prenatal maternal depression symptoms were not independently associated with more toddler behavioural problems, but that the association was mediated through decreased maternal sensitivity and through increased maternal depression symptoms 24 months postpartum (Edwards and Hans 2016). Three studies assessed child behaviour around the age of 3.5 years, and showed associations between elevated prenatal maternal depression symptoms and increased child internalizing and externalizing behaviour (Lahti et al. 2017) as well as a 2.8-times higher odds for clinically significant ADHD symptoms in the children (Wolford et al. 2017). Suarez et al. showed an association between high prenatal maternal depression symptoms and more child internalizing problems (only in boys), which was partly mediated by epigenetic gestational age (defined as the arithmetic difference between the ‘epigenetic age’ as defined by DNA methylation profiling of specific CpG sites in cord blood and chronological age) (Suarez et al. 2018). Interestingly, in line with observations from studies on child behaviour, one study also demonstrated the importance of the trajectory of depression symptoms across pregnancy (and after) on child cognitive function (table 4). They showed that high CES-D scores existing in pregnancy only were not associated with child IQ. However, compared to children of women who were never depressed, children of women with persistent high levels of depression symptoms had substantially lower Verbal, Performance, and Full Scale IQ (van der Waerden et al. 2017).

* 1. **Beck Depression Inventory revised (BDI-II)**

The Beck Depression Inventory revised (BDI-II) is a widely used, self-reported, well-validated, 21-item, clinical measure of severity of depression (Beck et al. 1961). Two studies used the BDI-II as a screening tool (table 4), and one study used the BDI-II in combination with two other tools (Phua et al.,described in section 3.1). Hermansen et al. compared three groups; one group of children born to women with a clinical depression during pregnancy without medication, one group of children born to women with a clinical depression during pregnancy with medication (SSRI), and a group of children born to non-depressed women. They observed a tendency of increased externalizing behavioural symptoms in children born to women with a clinical depression, either with or without medication, compared to non-depressed women, but they did not show a difference in IQ at the age of 5-6 years (Hermansen et al. 2016). One Ukranian study could not detect an independent association between prenatal depression symptoms and child cognitive function either, but did show an interaction between alcohol consumption in pregnancy and depression symptoms, indicating that higher prenatal maternal depression symptoms were associated with poorer child cognitive function in women that also used alcohol (Bandoli et al. 2016). It must be noted that in this study, as well as in most other studies included in this review, the mean symptom score for depression was (substantially) below the clinical cut-off values used to indicate depression, which may have led to an underestimation of the effect of an actual clinical depression in pregnancy on child behaviour and cognitive function.

* 1. **Other screening tools**

A remainder of three studies all used a different assessment scale to measure depression symptoms in pregnant women; the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos 1983), the Symptom Checklist (SCL) (Derogatis et al. 1976) or a self-reported diagnosis of depression in pregnancy (table 4). In summary, these studies reported that increased depression symptoms in pregnancy independently predicted more child hyperactivity at age 4 (Vizzini et al. 2018), as well as increased internalizing and externalizing behavioural problems between the age of 3 and 6 years old (Cents et al. 2013). However, in one very large study, after sibling comparison, only concurrent maternal depression was significantly associated with internalizing and externalizing behaviour (Gjerde et al. 2017).

* 1. **Intervention studies**

We identified four studies that assessed the effect of an intervention to reduce depression symptoms in pregnancy on child behaviour and/or cognitive function (table 3). One intervention included 43 structured lessons focusing on positive parenting, maternal behaviour and mental health, starting in late pregnancy and continuing up to 36 months postpartum. Women in the intervention group showed greater parenting knowledge and locus of control as well as decreased depression symptoms and drug abuse. Moreover, their children had fewer externalizing, internalizing and dysregulation problems at the age of 3 years (Barlow et al. 2015). In two small pilot studies, Cognitive Behavioural Therapy (CBT) was compared with Treatment as Usual (TAU) to reduce depression symptoms in pregnancy (Milgrom et al. 2015; Netsi et al. 2015). Milgrom et. al not only demonstrated beneficial effects of the intervention on maternal depression and anxiety symptoms, but also on problem solving, self-regulation and stress reactivity in the infants at 9 months of age (Milgrom et al. 2015). Netsi et al. compared CBT and TAU treatment for depression in pregnant women as well, but could not detect a significant difference in the outcome, child sleeping behaviour, between both groups. However, they did show that a reduction in depression symptom score was associated with easier temperament and shorter nocturnal sleep duration in the infants, which was more pronounced in the CBT compared to the TAU group (Netsi et al. 2015). Lastly, a home visiting intervention program plus standard care in pregnant women with a depressed mood was shown to result in 10.3% fewer children with very low cognitive scores on the Bayley Scales of development (> 2 standard deviations from the mean), compared to children born to women receiving standard clinic care (Tomlinson et al. 2017).

* 1. **Conclusion**

Although some studies reported independent associations between prenatal depression and increased internalizing and externalizing behaviour, more hyperactivity and poorer cognitive function after adjusting for confounding factors, some studies did not. The dissimilarities in study results likely arise from differences in study populations, assessment tools and different ages of the children at the behavioural or cognitive assessment. Overall, the study results suggest that the largest effects of elevated depression symptoms on child behaviour and cognitive function are seen in children of women with increasing and persistently high symptoms, followed by stable subclinical symptoms, compared to women with declining, few or no symptoms during pregnancy. Treatment of depression in pregnancy appears to improve behaviour and cognitive function in children up to 3 years old, although this is potentially mediated by improvements in parenting skills.

1. **Underlying mechanistic pathways**

Although the evidence is not fully conclusive, it seems likely that being depressed or malnourished in pregnancy contributes to suboptimal child behaviour and cognitive function. Both factors show associations with increased externalizing behavioural and attentional problems in the children, and to some extent with poorer cognitive function, which indicates that both factors may affect similar biological processes in the maternal-fetal compartment. Both malnutrition and depression represent a state of relative homeostatic ‘imbalance’, and the body may typically respond in terms of physiologic and biochemical alterations in order to restore homeostasis. These perturbations in maternal physiology with subsequent biochemical changes may then either 1. directly affect the developing embryo prior to implantation (Chason et al. 2011), 2. affect the process of placental development, implantation, and/or function (Jansson and Powell 2007), or 3. cross the placenta and enter the fetal circulation or amnion cavity with potential effects on cell and tissue development. In humans, a number of shared pathways linking malnutrition in pregnancy and/or elevated depression symptoms in pregnancy to increased child behavioural problems and/- or reduced cognitive function have been suggested, of which we will briefly highlight some in this paragraph.

* 1. **HPA-axis**

Dysregulation of the HPA-axis, potentially leading to increased (placental transfer) of cortisol may negatively impact child neurodevelopment. Activation of the HPA-axis typically occurs in stressful physiological or psychological situations, which may apply to either a state of nutritional shortage or excess, or chronic activation in case of depression. Modest associations between high depression symptoms in pregnancy and increased basal as well as stress-induced cortisol levels have been described in some studies (Murphy et al. 2015; O'Connor et al. 2014; O'Donnell et al. 2013), but not all (Bleker et al. 2017; van den Heuvel et al. 2018). Some studies concurrently report an association between elevated prenatal maternal depression symptoms and increased infant cortisol responses (Fernandes et al. 2015; Laurent et al. 2013; Thomas et al. 2017), which sometimes has also been linked to increased child emotional reactivity (Braithwaite et al. 2017; Swales et al. 2018), and poorer cognitive function (Grant et al. 2015). HPA-dysregulation has also been shown to occur in obese individuals. It has been reported that obese individuals with insulin resistance exhibit elevated cortisol levels compared to lean individuals (Bjorntorp 1995), but also blunted cortisol responses to stress (Carroll et al. 2017).

* 1. **Immune system**

Both obesity and depression may induce inflammation, which in pregnancy, may lead to a trans-placental transfer of antibodies or cytokines to the developing fetus. Also, clinical studies have shown altered cytokine levels in women with depression symptoms (Buglione-Corbett et al. 2018; Karlsson et al. 2017). In addition, expansion of adipose tissue mass as well as eating a high fat diet has been shown to lead to the recruitment and activation of immune cells (Ferrante 2013).

* 1. **Epigenetics**

Associations between prenatal depression and DNA methylation of genes have been described for cord blood *OXTR* (Unternaehrer et al. 2016)*,* placental *HSD11beta2* (Seth et al. 2015) and cord blood *NR3C1* (Oberlander et al. 2008). Interestingly, although this was only studied in animals, prenatal undernutrition also led to changes in *NR3C1* methylation levels in the offspring (Begum et al. 2013), suggesting that both conditions may act upon modifying methylation of the same genes. In addition, in offspring of sheep fed a high fat-diet during pregnancy, alterations in DNA methylation levels were seen in dopamine and opioid-related genes, which play a role in the reward circuitry (Vucetic et al. 2010), which also has been proposed to contribute to the pathophysiology and symptomatology of depression and may even be involved in its etiology (Nestler and Carlezon 2006).

* 1. **Oxidative stress**

Oxidative stress can be generated by several conditions, and the fetal brain is highly sensitive to injury to oxidant molecules (Dennery 2007). Increased reactive oxidant molecules may therefore act as a common pathway through which elevated depression symptoms and malnutrition in pregnancy may eventually impact fetal neurodevelopment. Clinical studies have shown that depressed pregnant women had decreased antioxidant levels compared to healthy counterparts (Camkurt et al. 2016). Another study showed that Malondialdehyde and nitric oxide levels (markers for oxidative stress) levels in newborns increased with maternal pre-gestational BMI, suggesting that maternal obesity before pregnancy increases oxidative stress in the offspring (Gallardo et al. 2015). Also, the type of diet can influence the level of oxidative stress as a diet high in saturated fats increases the level of oxidative stress, whereas vegetables and fruits decrease this level because they contain high levels of antioxidants (Wu et al. 2004).

1. **General discussion**

Although the number of studies examining either malnutrition or depression symptoms in pregnancy and child behaviour and/or cognitive function has increased over the past 5 years, studies that explicitly aimed to address both factors in terms of their interaction and interrelation in association with child behaviour and cognitive function, are still scarce. These factors are likely to share pathways which eventually may lead to increased child behavioural problem and poorer cognitive function. Adverse effects of maternal malnutrition in pregnancy, defined as an ‘unhealthy diet’, a deficiency in micronutrients, overweight/obesity on child externalizing and hyperactivity symptoms have been shown in some studies. Nutritional interventions are mainly assessed in low income countries and included daily supplements of micronutrients. No beneficial effects of nutritional supplements were observed on child cognitive function. Associations between increased depression symptoms during pregnancy and increased internalizing and externalizing behavioural problems, more hyperactivity and poorer cognitive function in children have been described in many studies. However, adjustment for postnatal and familial confounding sometimes attenuated these associations, whereas in other studies an independent significant association remained. Interventions for depression during pregnancy included either Cognitive Behavioural Therapy or a multi-facetted supportive and educational programs. These trials have provided suggestive evidence for a beneficial effect of depression treatment during pregnancy on child behaviour and cognitive function, although this is possibly (partly) mediated by improvement in postnatal parenting skills. Some potentially shared mechanisms that may underlie the associations between malnutrition and/or depression in pregnancy with less optimal behavioural and cognitive outcomes in children include the HPA-axis, the immune system, epigenetics and oxidative stress. With this review we aimed to provide an overview of recent studies that examined both nutrition and depression in pregnancy and their associations with child behaviour and cognitive function, and to elaborate on underlying mechanisms and the potential of interventions. The study has some limitations. We did not perform a systematic search and therefore some articles may have been missed in this review. Also, because of the abundance of literature, we decided to narrow down our search to include only behavioural and cognitive child outcomes and we did not include studies that investigated the effects of malnutrition and/or depression in pregnancy on other important developmental and psychopathological outcomes, such as motor development, autism, or schizophrenia. Lastly, antidepressant use during pregnancy may confound the associations described between increased depression symptoms in pregnancy and more child behavioural problems and/or poorer cognitive function, which was not addressed in most studies. One study specifically distinguished women with a clinical depression in pregnancy with or without medication use and showed an association with increased externalizing behavioural problems in children for both groups compared to women without depression symptoms in pregnancy, indicating an independent contribution of depression on the prevalence of child behavioural problems (Hermansen et al. 2016). Another study showed that exclusion of women that had been using an antidepressant during pregnancy did not alter the results (Suarez et al. 2018). Three other studies others included antidepressant use as a covariate in the analyses, which did not alter the results in two studies (Lahti et al. 2017; Wolford et al. 2017). Van der Waerden et al. showed no association between prenatal depression and offspring behaviour after adjusting for a set of covariates including antidepressant use, but the independent contribution of the covariates were not examined (van der Waerden et al. 2015).

1. **Conclusion**

Depression and malnutrition in pregnancy both show associations with externalizing behavioural problems and attentional deficits and to some extent with poorer cognitive function in the children, although the evidence is not conclusive. Interventions that aim to reduce maternal depression in pregnancy have shown to improve cognitive function and decrease behavioural problems in the children on the short-term, but for nutritional supplements no beneficial effects on cognitive function has been shown. Potential shared mechanisms include the HPA axis, the immune system, epigenetics, and oxidative stress. Only one study specifically examined synergistic effects of both factors on child behavioural problems, and more research is needed to gain more insight into the potential detrimental double burden for the developing child. Studying both factors simultaneously in future prospective or intervention studies is therefore highly recommended.

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LB wrote the manuscript, TR and SR provided comments on earlier versions of the paper and assisted in revising the manuscript.

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**Conflict of Interest**

The authors declare no conflict of interest.

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**Table 1.** Depression and nutrition in pregnancy and child behaviour and/or cognitive function

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Country** | **Year** | **N** | **Exposure/nutrient** | **Definition** | **Weeks Gestational Age (GA)** | **Behavioural or Cognitive Assessment** | **Age at outcome** | **Main Findings** |
| Barker et al. | UK | 2013 | 6.979 | Depression and nutrition | EPDS & FFQ | Between 32 weeks GA and 33 months postpartum | WISC-III | 8 years | Maternal prenatal depression symptoms were related to a more unhealthy diet, which, in turn, was prospectively associated with reduced child cognitive function (b = –0.010; 95% CI –0.015 to –0.006). |
| Micali et al. | UK | 2014 | 8.622 | Undernutrition and mood | EPDS & self-reported lifetime anorexia nervosa (AN) or bulimia nervosa (BN) in pregnancy | 12 weeks GA | SDQ | 3.5 years | More emotional, conduct, and hyperactivity disorders in female children of AN women [Odds Ratio (OR): 1.7 (95% Confidence Intervals 1.0–3.0); OR: 2.2 (1.2–4.0); OR: 1.8 (1.1–3.1), respectively] and more emotional disorders in male children [OR: 2.0(1.2–3.4)]. More hyperactivity in female children of BN women [OR: 1.7 (1.0–3.1)]; and more emotional and conduct disorders in male children of BN women [OR: 2.2 (1.2–3.9); OR: 2.4 (1.4–4.2), respectively]. Pregnancy anxiety and depression mediated the effect of maternal eating disorders on child psychopathology (RMEA= 0.02, CFI= 0.99, *p* < 0.01) |
| Munoz-Rocha et al. | Mexico | 2018 | 473 | Depression and manganese status | EDS & manganese levels in maternal blood during pregnancy and in cord blood | 3rd trimester | BSID-II | 24 months | 3rd trimester blood manganese as well as depression symptoms were independently negatively associated with all neurodevelopment scores. The negative association between manganese and language scores was stronger among women with depression symptoms. (Interaction terms : cognitive β = −0.08 p = 0.25, language β = −0.25 p < 0.01, motor β = −0.10 p = 0.89) |
| Pina-Camacho et al. | UK | 2015 | 7.814 | Depression and an unhealthy diet | EPDS & FFQ | 18 & 32 weeks GA | SDQ | 2, 4 and 7 years | Higher prenatal maternal depression symptoms were prospectively associated with higher unhealthy diet, both during pregnancy and the postnatal period, which, in turn, was associated with higher child dysregulation up to 7 years of age. In addition, during pregnancy, higher maternal depression symptoms and unhealthy diet were each independently associated with higher child dysregulation up to the age of 7 years. (RMSEA= 0.55, CFI= 0.91, *p* < 0.0001) |

**BSID-II =** Bayley Scales of Infant Development, **E(P)DS =** Edinburgh (Postnatal) Depression Scale, **FFQ** = Food Frequency Questionnaire, **SDQ =** Strengths and Difficulties Questionnaire**, WISC-III =** Wechsler Intelligence Scale for Children

**Table 2.** Nutrition in pregnancy or (pre-) pregnancy BMI and child behaviour and/or cognitive function

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Country** | **Year** | **N** | **Exposure/nutrient** | **Weeks Gestational Age (GA)** | **Behavioural or cognitive assessment** | **Age at outcome** | **Main findings** |
| **Diet** | | | | | | | | |
| Galera et al. | France | 2018 | 1.242 | Unhealthy Diet | 3r trimester, retrospectively | SDQ | 3,5,8 years | A ‘low healthy diet’ in pregnancy (OR = 1.61, 95% CI 1.09 to 2.37) as well as a ‘high Western diet’ (OR = 1.67, 95% CI 1.13 to 2.47) was associated with children’s trajectories of high hyperactivity-inattention symptoms |
| Jacka et al. | Norway | 2013 | 23.020 | Unhealthy Diet | 17 GA | CBCL | 1.5 years  3 years  5 years | More externalizing behavioural problems (fully adjusted intercept factor = 0.036, slope factor = -0.002, *p* <0.01) in children of women with an unhealthy diet |
| Steenweg-de Graaff et al. | Netherlands | 2014 | 3.104 | Diet type | 13.5 GA | CBCL | 1.5,3,6 years | A Mediterranean diet during pregnancy was negatively associated (OR per SD in Mediterranean score = 0.90, 95% CI 0.83 to 0.97), whereas a Traditionally Dutch diet was positively associated (OR per SD in Traditionally Dutch score = 1.11, 95% CI 1.03 to 1.21) with child externalizing problems |
| **(Micro-)nutrients** | | | | | | | | |
| Darling et al. | UK | 2017 | 7.065 | Vitamin D | 29.6 GA | ALSPAC test  SDQ  WISC | 6-42 months  7 years  8-9 years | Higher risk of scores in the lowest quartile for social development at 42 months (OR 1·20; 95 % CI 1·01, 1·41) in children of women with lower vitamin D. No association with cognitive function |
| Strom et al. | Denmark | 2014 | 850 | Vitamin D | 30 GA | ADHD diagnosis  Scholastic achievement | 22 years | No association with ADHD. No indication that maternal 25(OH)D serum concentrations <50 nmol/l were associated with a worse performance with regard to scholastic achievement |
| Morales et al. | Spain | 2015 | 1.650 | Vitamin D | 13 GA | ADHD | 4-5 years | Lower ADHD-like symptoms with increasing maternal 25(OH)D3 concentration (incidence rate ratio [IRR] = 0.89; 95% confidence interval [CI] = 0.80, 0.98) |
| Brouwer-Brolsma et al. | Netherlands | 2018 | 1.854 | Vitamin D | 13 GA | ANT | 5-6 years | Higher 25(OH)D status (nmol/l) was associated with better attention and executive functioning as shown by a faster reaction time (β −0·30 (sd 0·14) ms, P=0·03), faster response speed (β −0·58 (sd 0·21) ms, P=0·006), and better response speed stability (β −0·45 (sd 0·17) ms, P=0·009). No associations were observed of serum 25(OH)D with motor fluency and flexibility |
| Veena et al. | India | 2017 | 472 | Vitamin D | 30 GA | Kauffman Assessment Battery | 9-10 years &  13-14 years | No association with cognitive function |
| Steenweg-de Graaff et al. | Netherlands | 2015 | 6.999 | Fatty acid status | 20 GA | CBCL | 6 years | Higher ω-3: ω-6 ratio was associated with decreased odds of parent-reported (OR = 0.83, 95% CI 0.71 to 0.96) and combined parent/teacher-reported (OR = 0.77, 95% CI 0.65 to 0.92) child emotional problems |
| **(Pre-)Pregnancy BMI** | | | | | | | | |
| Daraki et al. | Greece | 2017 | 722 | Pregnancy BMI | 12 GA | SDQ  ADHD test  McCarthy | 4 years | Increased behavioural difficulties (β = 1.22, 95% CI 0.09 to 2.34), and ADHD symptoms (β = 4.28, 95% CI 1.20 to 7.36) in children of women with higher pre/pregnancy BMI. Lower cognitive ability (β = -4.03, 95% CI -7.08 to -0.97), perceptual performance (β = -4.60, 95% CI -7.74 to -1.47), quantitative ability (β = -4.43, 95% CI -7.68 to -1.18), and executive functions (β = -4.92, 95% CI -8.06 to -1.78) in children of women higher BMI |
| Antoniou et al. | UK | 2014 | 443 | Pre-pregnancy overweight | Not Reported | CBCL | 5 years | More aggressive and externalizing behavioural problems (OR = 1.10, 95% CI 0.58 to 2.06) in children from overweight women |
| Jo et al. | USA | 2015 | 1.311 | Pre-pregnancy BMI | Not Reported | SDQ | 6 years | More emotional symptoms (OR = 2.24, 95% CI 1.27 to 3.98), peer problems (OR = 2.07, 95% CI 1.26 to 3.40), total psychosocial difficulties (OR = 2.17, 95% CI 1.24 to 3.77), attention-deficit/hyperactivity disorders (ADHD) (OR = 4.55, 95% CI 1.80 to 11.46), autism or developmental delay (OR = 3.13, 95% CI 1.10 to 8.94) and speech language problems (OR =1.93, 95% CI 1.18 to 3.15) in children of women with higher pre-pregnancy BMI |
| Mina et al. | UK | 2017 | 112 | Obesity in pregnancy | Not Reported | SDQ  CBCL | 3-5 years | More hyperactivity, sleep problems, conduct problems, total difficulties, externalizing and total problems, anxious/depressed, aggressive behaviour and other problem syndrome scores and higher DSM-oriented affective, anxiety and ADHD in children of women with obesity in pregnancy (all effect sizes between 0.49 and 0.75 increase in points on a developmental assessment) |
| Robinson et al. | Australia | 2013 | 2.900 | Pre-pregnancy BMI | Not Reported | CBCL | 5,8,10,14 and 17 years | More affective problems in children from overweight (OR = 1.51, 95% CI 1.08 to 2.12) and obese (OR = 1.72, 95% CI 1.11 to 2,67) women |
| Bliddal et al. | Denmark | 2014 | 1.783 | Pre-pregnancy BMI | Not Reported | WPPSI | 5 years | BMI was inversely associated with child IQ with a decrease of 0.40 IQ point (−0.64 to −0.17) for every unit increase in BMI. This association was attenuated after adjustment for social factors and maternal IQ to −0.30 IQ points (−0.51 to −0.08), and paternal BMI showed a similar association |
| Casas et al. | Spain & Greece | 2013 | 1.967 (Spain)  412 (Greece) | Pre-pregnancy overweight and obesity | Not Reported | BSID-II | 11-22 months | Reduced infant cognitive development scores at 11-22 months in both the Spanish (score reduction = -2.27, 97% CI -5.35 to -0.10) and the Greek cohort (score reduction = -3.71, 95% CI -8.45 to 1.02) in children of women with pre-pregnancy overweight/obesity |
| Pugh et al. | USA | 2016 | 574 | Pre-pregnancy BMI | Not Reported | WRAT-R  WIAT | 6-10 years  14 years | Mothers with BMI values of 26,28 or 30 kg/m2 had children with math scores that were -1.3 (95% CI -2.2 to -0.4), -1.9 (95% CI -2.2 to -0.4), -2.6 (95% CI -2.2 to -0.4), points lower, respectively, compared with children whose mothers had a BMI of 22 kg/m2 |
| **Famine** | | | | | | | | |
| Li et al. | China | 2015 | 2.214 | Prenatal famine | Various trimesters | TMT  SCWT | Around 50 years | Prenatal exposure to famine was associated with a 8.7 (95% CI 6.5 to 10.9) second increase in part A of TMT (TMT-A); a 7.7 (2.3 to 13.1) second increase in part B of TMT (TMT-B); and a 6.1 (−7.7 to −4.5) score decrease in SCWT in adulthood |

**ADHD** = Attention Deficit Hyperactivity Disorder, **ALSPAC** = Avon Longitudinal Study of Parents and their Children**, ANT**  = Attention Network Test, **BSID-II =** Bayley Scale of Infant Development, **CBCL =** Child Behaviour Checklist, **TMT =** Trail Making Test**, SDQ** = Strengths and Difficulties Questionnaire, **SCWT =** Stroop Color and Word Test, **WIAT =** Wechsler Individual Achievement Test, **WISC-III =** Wechsler Intelligence Scale for Children, **WPPSI** = Wechsler Preschool and Primary Scale of Intelligence, **WRAT-R =** Wide Range Achievement Test - Revised

**Table 3.** Trials investigating the effect of nutritional and/or psychological interventions in pregnancy on child behaviour and/or cognitive function

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Country** | **Year** | **N** | **Intervention** | **Timing** | **Behavioural or cognitive Assessment** | **Age at outcome** | **Main findings** |
| **Nutrition** | | | | | | | | |
| Christian et al. | Bangladesh | 2016 | 734 | multiple micronutrient (MM) supplementation | Daily, from 10 GA | BSID-II | 24 months | No difference between groups |
| Dulal et al. | Nepal | 2018 | 813 | multiple micronutrient (MM) supplementation | Daily from 12 GA | FSIQ  EF | 12 years | No difference between groups |
| Prado et al. | Ghana | 2016 | 1.320 | iron/folic acid capsule (IFA), capsule containing 18 micronutrients (MMN), or 20g SQ-LNS | Daily, from <20 GA and to children until 6 months postpartum | KDI  MacArthur-Bates CDI  PSED  A not B task | 6,12,18 months | No effects on executive function |
| Prado et al. | Malawi | 2016 | 869 | small-quantity lipid-based nutrient supplements (SQ-LNSs) | Daily, from <20 GA and to children aged 6-18 months | KDI  MacArthur-Bates CDI  PSED  A not B task | 6,12,18 months | No effects on executive function |
| Srinivasan et al. | Bangalore | 2017 | 178 | oral B12 supplementation (50 µg) | <14 weeks of gestation through a 6-week post-partum | BSID-III | 9 months | No significant effects |
| **Depression** | | | | | | | | |
| Barlow et al. | USA | 2015 | 322 | 43 structured lessons incl. positive parenting, maternal behaviour and mental health | weekly through the third trimester of pregnancy, biweekly until 4 months postpartum, monthly between 4 and 12 months postpartum, and bimonthly between 12 and 36 months postpartum | Infant-Toddler Social and Emotional Assessment | 2, 6, 12, 18, 24, 30, and 36 months postpartum | Fewer externalizing, internalizing and dysregulation problems at 36 months (effect sizes 0.23, 0.23 and 0.27 respectively) |
| Milgrom et al. | Australia | 2015 | 54 | Pregnancy adjusted Cognitive Behavioural Therapy | 8 sessions weekly during pregnancy | ASQ-3  ASQ-SE  IBQ-R | 9 months | More beneficial ‘problem solving’  (Cohen's *d* = 0.72, 95% CI 0.36 to 1.08), ‘communication’ (Cohen's *d* = 0.53 , 95% CI 0.27 to 0.80), and ‘falling reactivity/rate of recovery from distress’ (Cohen's *d* = 1.08, 95% CI 0.54 to1.62) scores favouring the intervention group |
| Netsi et al. | UK | 2015 | 25 | Cognitive Behavioural Therapy | 12 sessions during pregnancy | Infant Characteristics Questionnaire & | 2 months | No differences by treatment arm were evident. Improvement in depression scores during pregnancy was associated with easier temperament (β=-.45, p=.024) and shorter nocturnal sleep duration (β=-.58, p=.003), which was more pronounced in the intervention group |
| Tomlinson et al. | South-Africa | 2017 | 594 | Home visiting intervention | A minimum of 8 times during pregnancy | BSID-II | 18 months | The overall cognitive and motor scale scores were similar, but fewer children with Bayley scores ≤ 85 (OR = 3.18, 95%CI 1.23 to 8.21) |

**ASQ(-SE) =** Ages and Stages Questionnaire, **BSID-II =** Bayley Scale of Infant Development, **CDI =** Child Development Inventory**,** **EF =** Executive Functioning, **FSIQ =** Full Scale IQ, **IBQ-R =** Infant Behavioural Questionnaire – Revised, **KDI =** Knowledge and Distributed Intelligence, **PSED =** Personal, Social and Emotional Development

**Table 4.** Depression in pregnancy and child behaviour and/or cognitive function

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| **Author** | **Country** | **Year** | **N** | **Psychiatric Screening tool** | **% Symptomatic/ mean score** | **Weeks Gestational Age (GA)** | **Behavioural or cognitive assessment** | **Age at outcome** | **Main findings** |
| **EPDS** | | | | | | | | | |
| Fredriksen et al. | Norway | 2018 | 1.036 | EPDS | Mean = 4.50 | 21 GA | BSID-III  ITEA | 18 months | No independent association |
| GIallo et al. | Australia | 2015 | 1.085 | EPDS | Mean = 4.79 | 10-24 GA,  30-23 GA | SDQ | 4 years | Children of mothers in the minimal depression symptoms trajectory were reported to have fewer emotional–behavioural difficulties than children of mothers in the Subclinical Depression Symptoms trajectory (p < .001, Cohen’s d = .45, 95 % CI = 0.31–0.58), and increasing and persistently high symptoms trajectories (p < .001, Cohen’s d = .76, 95 % CI = 0.53–0.98) |
| Guyon-Harris et al. | USA | 2016 | 120 | EPDS | Mean = 12.77 | 3rd trimester | BITSEA  Toddler affect expression | 2 years | More total behavioural problems (r = 0.29) as well as increased internalizing problems (r = 0.20) in children of prenatally depressed women |
| Junge et al. | Norway | 2017 | 1.235 | EPDS | Mean = 4.70 | 32 GA | ASQ-SE | 2 years | More social-emotional problems (OR = 3.4, 95% CI 1.4 to 8.0) in children of prenatally depressed women |
| Kingston et al. | Canada | 2018 | 1.983 | EPDS | 4.7 to 6.4% | <25 GA,  34-36 GA | Behavioral Scales developed for the NLSCY | 3 years | Increased risk of physical aggression symptoms (OR 1.64, 95% CI 1.13 to 2.36) in children of prenatally depressed women |
| Korhonen et al. | Finland | 2014 | 191 | EPDS | 23% | 3rd trimester | CBCL  YSR | 16 years | More externalizing problems (*p* = 0.037, standardized effect size = 0.40 on the CBCL) in children of prenatally depressed women |
| Leis et al. | USA | 2014 | 2.891 | EPDS | 17% | 18-32 GA | SDQ | 10-11 years | In the final model, which controlled for sociodemographic and psychosocial characteristics in addition to other maternal mental health problems, prenatal depression was significantly associated only with teacher-reported hyperactivity (β= 0.41, SE= 0.14) |
| Jensen et al. | UK | 2014 | 6.979 | EPDS | Not reported | 32 GA | WISC TEA-ch SCS | 8 years | Lower Verbal IQ (r = -0.034), Performance IQ (r = -0.032) and social cognition (r = 0.080) in children of prenatally depressed women |
| Koutra et al. | Greece | 2013 | 223 | EPDS | Not reported | 28-32 GA | BSID-III | 18 months | Lower cognitive development (β coefficient = -5.45, 95% CI -10.44 to -0.46) in children of prenatally depressed women |
| Park et al. | Canada | 2018 | 147 | EPDS  HAMD | Mean = 3.40 to 3.63 | 3rd trimester | CBCL  HBQ  BRIEF | 3 years  6 years | More total, internalizing and externalizing problems at age 3 in children of mothers who had increasing depression symptoms over time (β = 10.3, p < 0.001; β = 9.1, p < 0.01; β = 9.7, p < 0.001, respectively) but not age 6. |
|  |  |  |  |  |  |  |  |  | Children of mothers in the increasing trajectory group had poorer executive functions at age 6 than those of mothers in the low group, as assessed by both the BRIEF (β = 5.2, p = 0.05) and accuracy on the HF task (β = − 0.1, p = 0.03). |
| Phua et al. | Singapore | 2017 | 1.066 | EPDS  BDI-II | Not Reported | 26 GA | ITSEA | 12 months | Positive mood was positively associated with social competences (r= 0.094 to 0.123, *p* <0.05) and negatively with aggressive behaviour (r = 0.132, *p* = 0.013) |
|  |  |  |  |  |  |  | BSID-II | 12 months | Positive mood was positively associated with cognitive, language (i.e., receptive and expressive languages), social–emotional, and motor components (r = 0.111 to 0.136, *p* <0 .05) |
| Van Batenburg-Eddes et al. | UK | 2013 | 3.442 | EPDS | Not reported | 18 GA | SDQ | 4 years | More attentional problems (OR 1.33, 95% CI 1.19 to 1.48) in children of prenatally depressed women |
|  | Netherlands | 2013 | 2.280 | BSI | Not reported | 20 GA | CBCL | 3 years | After adjusting for maternal symptoms after giving birth, antenatal maternal depression and anxiety were no longer associated with child attention problems |
| **CES-D** | | | | | | | | | |
| Edwards et al. | USA | 2016 | 196 | CES-D | Mean = 15.8 | 27.6 GA | BITSEA | 24 months | Mediation by maternal sensitivity (r = -0.19) and through 24-months maternal depression symptoms (r = 0.52) in children of prenatally depressed women |
| Lahti et al. | Finland | 2017 | 2.296 | CES-D | 21.3% | 12-38 GA | CBCL | 3.5 years | More internalizing (0.28 SD unit per SD unit increase, 95% CI 0.24 to 0.32) and externalizing behaviour (0.26 SD unit per SD unit increase, 95% CI 0.23 to 0.30) in children of prenatally depressed women |
| Raskin et al. | USA | 2016 | 400 | CES-D | 40% | Across all trimesters | BITSEA | 24 months | More total behavioral problems (Sum score t(340) = -6.18, *p* < 0.005) in children of prenatally depressed women |
| Suarez et al. | Finland | 2018 | 407 | CES-D | Mean = 11.50 | Biweekly from 12 GA onward | CBCL | 3.7 years | Lower epigenetic gestational age, which partially mediated the effects of maternal antenatal depression on internalizing problems in boys (β = 0.04, 95%CI 0.001 to 0.15) |
| Van der Waerden et al. | France | 2015 | 1.183 | CES-D | Mean = 11.04 | 24-28 GA and further on | SDQ | 5 years | No independent association between prenatal depression and child behaviour. |
| Wolford et al. | Finland | 2017 | 1.779 | CES-D | 21.6% | Biweekly from 12 GA | CHI | 3.8 years | Children of mothers with consistently high depression symptoms showed higher average levels (mean difference = 0.46 SD units, 95% Confidence Interval [CI] 0.36, 0.56, p < 0.001 compared to the low group), and proportion (32.1% vs. 14.7%) and odds (odds ratio = 2.80, 95% CI 2.20, 3.57, p < 0.001) of clinically significant ADHD symptoms. |
| Van der Waerden et al. | France | 2017 | 1.039 | CES-D | Mean = 11.08 | 24-28 GA and further on | WPPSI-III | 5-6 years | No independent association between prenatal depression and child IQ |
| **BDI-II** | | | | | | | | | |
| Hermansen et al. | Norway | 2016 | 103 | BDI-II | Mean = 3.91 to 8.83 | 15 and 30 GA | NEPSY-II  CBCL | 5-6 years | A tendency of increased externalizing behavior (t (1,67) = −2.50, p = .014, η 2 = .09.) in children of prenatally depressed women |
| Bandoli et al. | Ukraine | 2016 | 344 | BDI-II | 21% | 32 GA | BSID-II  WPPSI | 6 and 12 months | No evidence that un-medicated maternal depression symptoms independently predicted neurodevelopmental outcomes. No differences in IQ |
| **Mixed or other** | | | | | | | | | |
| Cents et al. | Netherlands | 2013 | 4.167 | BSI | 1.5% | 20 GA | CBCL | 3 years | More internalizing (Overall β = 0.25, *p* <0.001) and externalizing problems (Overall β = 0.21, *p* <0.001) in children of prenatally depressed women |
| Gjerde et al. | Norway | 2017 | 17.830 | SCL | Not reported | 17 & 30 GA | CBCL | 5 years | After sibling comparison, only concurrent maternal depression was significantly associated with internalizing [estimate = 2.82 (1.91-3.73, 95% CI)] and externalizing problems [estimate = 2.40 (1.56-3.23, 95% CI)] |
| Vizzini et al. | Italy | 2018 | 3.634 | Self-reported diagnosis of depression | 1.9% | 26 GA | mother-reported symptoms of ADHD | 4 years | More inattentive and hyperactive–impulsive symptoms (17.5%; 95% CI 3.2-33.8%) in children of prenatally depressed women |

**ASQ(-SE) =** Ages and Stages Questionnaire (– Social Emotional Development), **BDI-II** = Beck Depression Inventory, **BITSEA =** Brief Infant-Toddler Social and Emotional Assessment, **BRIEF =** Behavior Rating Inventory of Executive Function, **BSI** = Brief Symptom Inventory, **BSID-III =** Bayley Scale of Infant Development, **CBCL =** Child Behaviour Checklist, **CES-D** = Center for Epidemiologic Studies – Depression, **CHI =** Connor’s Hyperactivity Index, **E(P)DS** = Edinburgh (Postnatal) Depression Scale, **HAMD** = Hamilton Depression Rating Scale, **HBQ =** Health Behaviour Questionnaire, **NEPSY-II =** A Developmental Neuropsychological Assessment, **NLSCY =** National Longitudinal Survey of Children and Youth, **SCL** = Symptom Checklist**, SDQ =** Strengths and Difficulties Questionnaire, **TEA-ch =** Test of Everyday Attention for Children, **WISC =** Wechsler Intelligence Scale for Children, **WPPSI** = Wechsler Preschool and Primary Scale of Intelligence, **YSR =** Youth Self Report