Title: Maternal psychological distress during pregnancy and childhood health outcomes: a narrative review

Short title: Prenatal stress and child health outcomes

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Abstract

Maternal psychological distress is common in pregnancy and may influence the risk of adverse outcomes in children. Psychological distress may cause a suboptimal intrauterine environment leading to growth and developmental adaptations of the fetus and child. In this narrative review, we examined the influence of maternal psychological distress during pregnancy on fetal outcomes and child cardiometabolic, respiratory, atopic and neurodevelopmental-related health outcomes. We discussed these findings from an epidemiological and life course perspective and provided recommendations for future studies. The literature in the field of maternal psychological distress and child health outcomes is extensive and shows that exposure to stress during pregnancy is associated with multiple adverse child health outcomes. Because maternal psychological distress is an important and potential modifiable factor during pregnancy, it should be a target for prevention strategies in order to optimize fetal and child health. Future studies should use innovative designs and strategies in order to address the issue of causality.

Keywords Maternal psychological distress, pregnancy, child health, narrative review
Introduction

Although pregnancy should be a period of happiness and excitement, 10-20% of pregnant women experience psychological distress.\textsuperscript{1-5} Psychological distress can be described as general stress, depressive symptoms, anxiety or experiencing an adverse life event.\textsuperscript{6-8} Poverty, low socioeconomic status and single status are some of the risk factors for psychological distress during pregnancy.\textsuperscript{9} Studies suggest that maternal psychological distress during pregnancy can have adverse consequences on the development of their child.\textsuperscript{10-17} Maternal psychological distress during pregnancy may lead to fetal and postnatal adaptations through intrauterine mechanisms.\textsuperscript{18-20}

Experiencing psychological distress by the mother could attribute to a suboptimal fetal environment and may co-occur or interact with adverse lifestyle factors including smoking, alcohol and under- or overnutrition.\textsuperscript{14, 21-25} The developing fetus adapts to suboptimal conditions during critical periods of pregnancy by structural and functional changes in cells, organs and tissues.\textsuperscript{10} These developmental alterations may have long-term consequences and affect health throughout life. Optimizing maternal and pregnancy health is thus of great importance to improve wellbeing of their children throughout life.

In this narrative review, we provide an update of the findings from recent observational studies and meta-analyses focused on the associations of maternal psychological distress during pregnancy including i.e. general stress, depressive symptoms, anxiety or experiencing an adverse life event with fetal outcomes and cardiometabolic, respiratory, allergy and neurodevelopmental outcomes throughout childhood, Fig 1. These health outcomes are known risk factors for NCDs in later life.\textsuperscript{26-31} We searched for relevant articles per outcome in the online databases Google Scholar and PubMed using MeSH (Medical Subject Headings) terms of the National Library of Medicine (NLM). We also discuss potential mechanisms underlying the observed associations, causality and challenges for future research. Insight in maternal psychological distress during pregnancy and adverse child outcomes is of great
importance, as maternal mental health could be a modifiable target for prevention to improve both maternal and offspring wellbeing.

Fetal and birth outcomes

Maternal psychological distress has repeatedly been related to fetal growth using ultrasound measures. In an explorative study of 91 pregnant women maternal depressive symptoms during pregnancy were associated with smaller fetal head circumference in the third trimester, but anxiety symptoms were not. In a case-control study, it was shown that maternal depressive and anxiety symptoms in pregnancy were related to intrauterine growth restriction of the child. Further, in a study that used ultrasound measures in pregnancy, no differences in ultrasound measures at 20 and 34 weeks of gestation (including abdominal circumference, head circumference and femur length) were found, but this study did show that children exposed to maternal depression and/or anxiety had a lower mean birth weight. Another case-control study examined fetal growth rates by using estimated fetal weight at 18-20 weeks and birth weight, and reported a lower estimated fetal weight in mid-gestation and slower fetal growth rate during the second half of pregnancy in fetuses exposed to maternal depressive symptoms. Likewise, in the Generation R study, a prospective population-based multi-ethnic cohort study, ultrasound measures during pregnancy were collected repeatedly and growth trajectories were used in a very large sample of pregnant women. In this study, maternal psychological distress during pregnancy was associated with decreased fetal growth. However, studies are not always consistent. Some studies reported no association of prenatal maternal psychological distress with fetal growth or birth outcomes. For example, in a prospective observational study prenatal maternal depression was associated with preterm birth but not with birth weight. Interestingly, a meta-analyses on this topic showed that women with depression during pregnancy are at increased risk for
children born preterm born and with a low birth weight, but the results should be interpreted with caution because of different magnitudes of effect, ethnicities and socioeconomic status per study.\textsuperscript{40} Further, another meta-analysis of 15 studies on maternal anxiety during pregnancy and birth outcomes found that maternal anxiety is associated with an 1.5 increased risk of low birth weight as well as an increased risk of 1.8 of preterm birth.\textsuperscript{41} Thus, the current literature suggests that exposure to maternal psychological stress affect fetal growth and birth outcomes, but remains inconsistent, see Table S1.

**Child outcomes**

**Cardiometabolic outcomes**

Cardiometabolic health of children might be affected by maternal psychological distress during pregnancy. Maternal psychological distress in pregnancy has been associated with an increased risk of child’s adiposity.\textsuperscript{42} A potential pathway might be that maternal psychological distress during pregnancy is associated with birth weight of children and subsequent catch-up growth during infancy. Birth weight and catch-up growth are both strong risk factors for later overweight and obesity.\textsuperscript{43} In a study among 65,212 mother-child pairs, 10-13-year old children exposed to prenatal stress, defined by being born to mothers who were bereaved by death of a close family member, had an increased risk of overweight.\textsuperscript{44} Additionally, a prospective cohort study among 838 mothers and their children showed that depression of the mother during pregnancy was associated with adiposity but a lower body mass index (BMI) at age 3 years.\textsuperscript{45} Several studies found that women exposed to an adverse life event, either maternal bereavement or a natural disaster, had a significantly increased risk of children with adiposity.\textsuperscript{46-48} Furthermore, parental separation before childbirth has been associated with an increased risk of overweight and obesity at the age of 9-11 years.\textsuperscript{49} However, large population studies did not find consistent associations between prenatal
maternal stress and adiposity measurements in childhood. For example, in the Generation R study, we observed no association between prenatal maternal depression and child BMI at several measurements between age 3 months to age 4 years. Furthermore, in a large study among 37,764 Danish women and child pairs, self-reported stress, depressive or anxiety symptoms at around 30 weeks of gestation were not associated with childhood overweight at 7 years of age. Interestingly, two large prospective cohort studies found no consistent associations between antenatal maternal depression and child growth, but suggested child sex-specific effects of prenatal maternal stress.

Moreover, an association between maternal psychopathology during pregnancy and increased fetal heart rate has been reported. However, this association, along with other cardiovascular outcome factors in childhood, was not found in two large prospective cohort studies. Although fetal exposure to increased glucocorticoid levels have been linked to adult hypertension, studies do not find an association between maternal psychological distress and child hypertension. However, one of these studies observed a non-significant association between prenatal stress and higher systolic and diastolic blood pressure in children. Thus, it might be that these altered blood pressures precede hypertension in later life.

Further, both low-grade chronic inflammation and insulin resistance are known to precede type 2 diabetes. A relation between maternal psychological distress and increased inflammatory markers during pregnancy, such as C-reactive protein (CRP) and interleukins, was shown. Animal studies suggest that prenatal maternal psychological stress has lasting effects on the immune system of offspring, but little is known about this effect on human offspring. Only one study reported increased interleukin-4 (IL-4) levels in children exposed to prenatal maternal anxiety. Studies on prenatal maternal psychological distress in relation to child glucose metabolism are also scarce. Both in young adults and adolescents at the average age of 13.5 years, prenatal psychosocial stress exposure was positively associated with insulin secretion and resistance. On the contrary, in 5-6 year old children
no associations of prenatal stress and glucose, C-peptide or insulin resistance were found, potentially because the relation was examined early in life. Further, young adults exposed to maternal prenatal stress had higher very low density lipoprotein and lower high density lipoproteins, suggesting differences in fat storage processes. To our knowledge no studies on the association between prenatal stress and lipid profile in childhood have been performed.

Most reviewed studies report that prenatal maternal distress is associated with increased risk for adverse cardiometabolic child outcomes, see Table S2. However, results are often inconclusive and need further investigation.

**Respiratory and atopic outcomes**

Prenatal exposure to psychological distress has been linked to respiratory and atopic outcomes in children. A meta-analysis found that children whose mothers experienced psychological distress during pregnancy had higher risks of childhood wheezing, asthma, or other respiratory morbidity. Thereafter, a large number of cohort studies have been published with more detailed data. Some studies assessed maternal anxiety and depression symptoms during pregnancy separately, while others examined overall psychological distress of the pregnant women, which also included hostility, somatic problems, or poor self-esteem among others besides anxiety and depression. Mixed results were observed when maternal anxiety or depression symptoms during pregnancy were examined separately in relation to child wheezing and asthma. However, overall psychological distress during pregnancy was consistently associated with wheezing and asthma. Other studies examined maternal psychological distress during pregnancy as bereavement or adverse life events, self-reported perceived stress, psychological job strain, or community violence with respiratory outcomes and showed an association of these...
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exposures with an increased risk of child wheezing, asthma or lower lung function.73, 76, 78-80, 87-103

Maternal psychological distress during pregnancy may also influence the risk of allergy and eczema in children.93 Birth cohort studies observed no associations of maternal psychological distress during pregnancy with childhood allergic sensitization (measured with skin prick tests) or physician-diagnosed food allergy.93, 104 However, maternal psychological distress during pregnancy were associated with an increased risk of physician-diagnosed inhalant allergy in children.104 These results were independent of maternal psychiatric symptoms after delivery, and of paternal psychiatric symptoms during pregnancy and after delivery. Other birth cohort studies used immunoglobulin E (IgE) levels to identify allergic sensitization.83, 93, 105-108 Some studies showed that maternal psychological distress during pregnancy was associated with increased umbilical cord blood IgE levels or serum allergen-specific IgE levels,105-108 while other studies observed no associations.83, 93 One birth cohort study combined data on food-specific serum IgE levels and on questionnaire obtained food allergy, and observed no association of maternal psychological distress during pregnancy with food allergy.83, 109 Furthermore, previous birth cohort studies have reported inconsistent results on the association of children of mothers with psychological distress during pregnancy with eczema.93, 94, 105, 106, 110-112 However, most studies showed that children who were prenatally exposed to maternal psychological distress had an up to 4-fold increased risk of eczema, compared with those unexposed.94, 105, 111, 112

Overall, maternal psychological distress during pregnancy appears to be associated with childhood respiratory and atopic health, see Table S3 and S4. However, it is unclear which specific respiratory and atopic outcome might be more affected, at what age, and what the long term effects into adulthood are.

Neurodevelopmental outcomes
A number of studies has focused on maternal psychological distress and neurodevelopmental outcomes from birth onwards. Newborns of depressed mothers show less responsiveness to stimulation. Children exposed to maternal psychological distress during pregnancy are more likely to show negative affectivity, and more excessive crying. Maternal psychological distress is also significantly related to attachment security. On the cognitive domain, children exposed to psychological distress in pregnancy have less advanced or delayed language development, and lower academic skills. Furthermore, children exposed prenatally to maternal psychological distress display altered stress reactivity in early childhood and increased sleep disturbances. Moreover, children exposed to maternal psychological distress during pregnancy are at increased risk to develop internalizing, such as depressive symptoms and being withdrawn. Finally, externalizing problems, such as aggressive behavior and attention deficit hyperactivity disorder symptoms are also more prominent in children exposed to maternal psychological distress during pregnancy. The underlying neurobiology of the reported associations is unclear, but evidence is accumulating. Several studies have shown that prenatal exposure to maternal depressive symptoms is related to differences in volumes and white matter microstructure of the limbic system in preschoolers and children aged 6 and 10 years. Additionally, prenatal maternal depression has been shown to alter the functional connectivity of the amygdala in early postnatal life. Further, using an exploratory approach rather than only the limbic system exposure to maternal depressive symptoms in pregnancy has been linked to cortical thinning of the frontal and temporal cortex of the brain in three recent studies. However, other studies found no or even positive associations of prenatal maternal psychological distress and child neurodevelopmental outcomes (e.g. school achievement, motor and language development). and thus these results must be interpreted with caution.

Finally, overall there is a consensus that maternal psychological distress is associated with developmental problems in children and adolescents, including impaired socio-
emotional, cognitive and behavioral functioning, however the underlying neurobiology needs further examination, also see table S5.139-141

**Underlying mechanisms**

The pathways through which maternal psychological distress during pregnancy may lead to adverse fetal and child outcomes are various and multifactorial, Fig 1.41 One of the most described underlying mechanism includes fetal exposure to increased cortisol levels due to altered activation of the maternal hypothalamic pituitary adrenal (HPA) axis in response to both physiological and psychological distress.142 146 Fetal exposure to excess cortisol may lead to altered programming of the fetal HPA axis, which in turn may be associated with adverse birth outcomes and could have long term child health consequences. 19, 142-150 A linear relation was shown between fetal and maternal cortisol concentrations.151 Cortisol stimulates corticotropin releasing hormone (CRH) secretion and production, resulting in positive maternal and fetal feedback loops and increased cortisol concentrations, potentially further amplifying the effect.152-154 Subsequently, the uteroplacental blood flow may be reduced in response to increased secretion of maternal cortisol and catecholamines,155 which may lead to fetal growth restriction and other adverse child health outcomes.152, 153 Animal studies on the association between excess catecholamines and fetal or child outcomes are conflicting,156-158 and human studies are scarce. Only one study reported high maternal catecholamine concentration to be associated with an increased risk of spontaneous preterm birth.159 However, studies are inconsistent about the relation between maternal psychological distress during pregnancy and maternal cortisol levels which needs further investigation.160-

163 A related mechanism is the functioning of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2), a placental enzyme that inactivates 50-90% of maternal cortisol.164, 165 Reduction of 11β-HSD-2 levels expose the fetus to higher levels of maternal cortisol. Clinical studies showed reduced placental 11β-HSD-2 gene expression in pregnancies with
intrauterine growth restriction and preterm birth.\textsuperscript{166, 167} Also, both clinical and animal studies have shown reduced gene expression and/or activity of placental 11ß-HSD-2 in association with maternal anxiety.\textsuperscript{166, 167}

Next to the HPA-axis as an underlying mechanism, the autonomic nervous system (ANS) is another physiological mechanism by which organisms react to stress.\textsuperscript{168} The ANS is responsible for regulation of several processes in the body such as respiration, digestion, body temperature and metabolism.\textsuperscript{169} In contrast to the role of the HPA-axis, the ANS as a possible mechanism is less extensively examined. However, ANS functioning has been described as a mediator in the association of prenatal maternal psychological distress and child health outcomes. For example, heart rate (HR) and heart rate variability (HRV) are regulated through ANS functioning and have been studied in relation to maternal prenatal distress.\textsuperscript{144} Maternal depression and anxiety have been associated with both a higher and a reduced baseline fetal heart rate.\textsuperscript{170-173} Results on the ANS are not conclusive and need further clarification.

Further, another possible mechanism underlying maternal stress during pregnancy and adverse child outcomes are epigenetic changes.\textsuperscript{174} Epigenetic changes are chemical modifications to chromatin that regulate genomic transcription.\textsuperscript{175} Studies showed that prenatal psychological distress could lead to changes in DNA methylation which subsequently may have a mediation effect on the association between prenatal maternal psychological distress and child health outcomes.\textsuperscript{175-183} Epigenetic changes of DNA methylation of the glucocorticoid receptor gene NR3C1 in cord blood and infant salivary samples are associated with maternal stress and could be responsible for the increase of the sensitivity of the fetal HPA axis.\textsuperscript{179, 184}

Another potential mechanism involves inflammatory responses to psychological distress during pregnancy.\textsuperscript{185} In animal studies, prenatal maternal stress has been shown to program postnatal immunity.\textsuperscript{186} Interestingly, higher circulating levels of pro-inflammatory cytokines in
pregnant women with psychological distress or depression have been reported. Further, elevations of inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in maternal serum, are associated with increased risk of fetal outcomes such as prematurity.

Additionally, the potential role of the maternal microbiome as a mechanism through which maternal psychological distress during pregnancy can affect the fetus and children should be considered. The microbiome could be defined as the community of microorganisms living in or on the human body. Studies found that the gut microbiome is essential for early development. The HPA axis and the central nervous system regulatory areas affect the gut microbiota composition, which may influence the pathogenesis of diseases. The bidirectional signaling pathways between the gut and brain, the so-called gut-brain axis, have been suggested to underlie neurodevelopmental and psychiatric disorders. Development of the gut microbiome, begins when the infant encounters the maternal vaginal and fecal bacteria during birth. Studies examining the association of maternal psychological distress during pregnancy and child microbiome are scarce. One recent study found an association between maternal stress and the infant intestinal microbiome.

Recently proposed mechanisms are exposure to oxidative stress and serotonergic system as well. Excessive oxidative stress exposure during human pregnancy has been associated with spontaneous abortion, intrauterine growth restriction (IUGR), preterm delivery and allergic diseases in the offspring. Evidence, especially in humans, for the involvement of serotonin and tryptophan in the maternal-fetal stress transfer is limited. Animal studies, however, provide preliminary evidence of a potential role for serotonin and tryptophan in fetal programming. Additionally, meta-analyses have shown that women with antenatal depression treated with selective serotonin reuptake inhibitors (SSRIs), medications that increase serotonin levels by blocking reuptake, have a significantly increased risk for preterm birth and low birth weight, and thus support the hypothesis of involvement of the serotonergic system.
In conclusion, the most described underlying mechanism of the association between maternal psychological distress and adverse outcomes in the offspring includes altered HPA-axis functioning but there is emerging evidence that other mechanisms also play a role.

Limitations

This review suggests that exposure to maternal psychological distress during pregnancy may be associated with long-term health and developmental outcomes from fetal life onwards. Nevertheless, there are several limitations that have to be considered. One of the difficulties with studies on maternal psychological distress during pregnancy and child outcomes is that (pregnancy-related) psychological distress is a very broad concept of which no specific scales are available. Maternal psychological distress during pregnancy refers to the mental or emotional strain resulting from adverse circumstances that pregnant women experience. Maternal psychological distress during pregnancy can be chronic or acute. Maternal psychological distress during pregnancy can be categorized in two types; objective stress (e.g. lack of food and water following a natural disaster) and subjective distress (i.e. an individual’s response to an event). There are many ways to assess psychological distress ranging from questionnaires, like the perceived stress scale, screening tools of psychopathology including depression and anxiety (e.g. Hospital Anxiety and Depression Scale (HADS), State-Trait Anxiety Inventory (STAI), Edinburgh Postnatal Depression Scale (EPDS), Beck’s Depression Inventory (BDI) or the Center for Epidemiological Studies-Depression Scale (CES-D), experiencing adverse life events, and exposure to natural disasters. Existing psychological distress scales differ and are not pregnancy-specific.

Moreover, some scales include somatic symptoms experienced by many pregnant women, such as nausea and vomiting, which could potentially lead to overestimation of the number of women with psychological distress.

It is possible to assess a number of biological markers in response to stress, including cortisol, adrenalin or cardiovascular measures such as heart rate, blood pressure.
Combining psychological distress with biological stress markers will be useful approaches to define psychological distress during pregnancy. For example, studies report associations between maternal cortisol during pregnancy and adverse child outcomes, but interpretation is difficult as study designs and cortisol assessment methods differ.

Further, because studies had different study designs; sample sizes and different age groups, we should interpret the results with caution. Further, timing and degree of both exposure and outcome need to be considered. Often studies have only assessed psychological distress once during pregnancy and no assessment before or after pregnancy are available, which makes interpretation of findings difficult. Studies are inconsistent with regard to the gestational age at which the effects of psychological distress during pregnancy are most pronounced.\textsuperscript{16, 151}

Finally, bias due to confounding can never be excluded in cohort studies. In the general population maternal psychological distress often co-occurs with risk behavior such as alcohol consumption, unhealthy diet and tobacco smoking, but also with poverty and separation.\textsuperscript{207-211} Psychological distress during pregnancy contributes to adverse maternal health behavior.\textsuperscript{23-25, 212, 213} If psychological distress continues to be present after birth, this risk behavior may still affect the development of the child through, for example, parenting and dietary habits.\textsuperscript{214-217} Most reviewed studies take into account available confounders, however residual confounding, for example by medication use, cannot be ruled out.

Recommendations for future research

This review shows that the literature on maternal psychological distress during pregnancy and offspring health outcomes is accumulating. Table 1 shows that children exposed to
maternal psychological distress are more likely to have a lower birthweight and increased risk for asthma, however evidence is insufficient for several cardiometabolic and neurodevelopmental outcomes, see table 1. Although many of the studies were longitudinal, had a relatively large sample size and took many confounding factors into account, the question whether these associations are causal or are confounded by related genetic and environmental factors remains not fully clear. It is important to know the causal nature of the associations to develop evidence-based guidelines for effective intervention and prevention programs. To address the issue of causality and to move forward in the field, we need innovative designs and strategies. A comparison of the effects of maternal and paternal depressive symptoms during pregnancy could uncover potential causal relationships between intrauterine and extrauterine exposures and offspring health.218 An intrauterine causal relationship should be detectable by a stronger association of maternal than paternal depressive symptoms during pregnancy with health outcomes in children. An equal association of maternal and paternal depressive symptoms during pregnancy with health outcomes might be explained by residual confounding of unmeasured factors. This approach has been used in a few recent studies,74, 75, 85, 87, 130, 134 but should be utilized more often. For example, in four studies with wheezing and asthma as an outcome, the investigators reported an association between maternal anxiety symptoms or overall psychological distress during pregnancy and wheezing or asthma, while no association was observed of paternal psychological distress during pregnancy with child respiratory morbidity.74, 75, 85, 87 However, assortative mating for psychiatric disorders - the tendency for women with psychological disorder to pair with men with psychological disorder and vice versa - is well known and a possible limitation.219, 220

Another possibility would be to use Mendelian randomization, a method that uses genetic variants as instrumental variables. These genetic variants are robustly associated with the exposure 221, and generate more reliable evidence regarding the causal relationship of maternal psychological distress during pregnancy and child health outcomes. Mendelian
randomization relies on the assumption that any association between the genetic instrument(s) and the health outcome is entirely mediated by the exposure (i.e., vertical pleiotropy).\textsuperscript{222, 223} However, the polygenic nature of complex traits, such as psychological distress, increases the probability of existing biological links between exposure-associated variants and the outcome not mediated by the exposure itself (i.e., horizontal pleiotropy).\textsuperscript{222, 223}

Further, little is known about the role of developmental timing - the idea that certain periods in fetal and child development when the child is particularly vulnerable to the impact of maternal psychological distress. A strong correlation between prenatal and postpartum maternal depression exists, which may have different effects on child development.\textsuperscript{45, 139, 224} Large longitudinal studies, preferably starting preconception, with repeated measures of psychological distress and repeated measures of child health and development are needed.

Randomized controlled trials (RCTs) of prenatal stress, which allow total control of the type, severity, and timing of the stressor in utero is unethical. However, RCTs of (non-pharmacological) treatment of prenatal psychological distress may give insight on the causal nature of psychological distress during pregnancy and child health outcomes. A recent randomized controlled trial showed that weekly exercise sessions during pregnancy reduce the level of depressive symptoms.\textsuperscript{225} The next step in such studies should focus on long follow-up of child health. Another type of design is studying women who experience natural disasters during pregnancy, as this may approximate the random assignment similar to randomization in animal studies. Several of these studies are ongoing and show an increased risk for adverse child outcomes for women exposed to a natural disaster, for example the Project Ice Storm, Iowa Flood Study and Queensland Flood Study.\textsuperscript{226} However, such studies have logistical challenges to face when initiating a study of pregnant women in the immediate aftermath of a natural disaster.
Another interesting design is adopted from prenatal cross-fostering animal studies, which allow the maternally provided prenatal environment and inherited factors to be disentangled. Previously, it has not been possible to study human children whose prenatal environment is provided by a biologically unrelated mother. This is now feasible, because of increased use of in vitro fertilization (IVF) as a mean of conception. Children conceived via IVF can be related to both parents (homologous IVF), the mother only (IVF with sperm donation), the father only (IVF with egg donation) or to neither parent (IVF with embryo donation). With egg and embryo donation, the mother provides the intrauterine environment but is not related to the child. These alternative designs can be useful in addressing the question of causality and mechanisms in the association of psychological distress during pregnancy and offspring health, although sample size might be an issue.

Finally, the combination of human studies together with animal studies could provide more insight in underlying mechanisms. Such studies could focus on a variety of aspects like epigenetic changes. Summarized, to address the issue of causality and to move forward in the field, innovative designs and strategies can be useful. However, these designs all have their own strengths and limitations, which must be kept in mind.

Conclusions

In this narrative review, we described that in many studies maternal psychological distress during pregnancy is associated with an increased risk for adverse fetal and child health outcomes. The most described underlying mechanism of these associations is fetal exposure to increased maternal cortisol levels, but there is emerging evidence that other mechanisms involving the maternal microbiome, epigenetics and inflammatory factors may also play a role. More detailed population-based prospective cohort studies, as well as intervention randomized controlled trials and Mendelian randomization studies, are needed to further investigate the causal effect of maternal psychological distress during pregnancy.
on fetal and child outcomes. Maternal mental health during pregnancy could be a modifiable
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Conflicts of Interest

None
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