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REVIEW ARTICLE

Prenatal risk factors for internalizing and externalizing problems in childhood

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Abstract

Background A growing body of research has documented the effects of prenatal risk factors on a wide spectrum of adverse offspring health outcomes. Childhood behavior problems, such as externalizing and internalizing problems, are no exception. This comprehensive literature review aims to summarize and synthesize current research about commonly experienced prenatal risk factors associated with internalizing and externalizing problems, with a focus on their impact during childhood and adolescence. Potential mechanisms as well as implications are also outlined.

Data sources The EBSCO, Web of Science, PubMed, Google Scholar, and Scopus databases were searched for studies examining the association between prenatal risk factors and offspring internalizing/externalizing problems, using keywords "prenatal" or "perinatal" or "birth complications" in combination with "internalizing" or "externalizing". Relevant articles, including experimental research, systematic reviews, meta-analyses, cross-sectional and longitudinal cohort studies, and theoretical literature, were reviewed and synthesized to form the basis of this integrative review.

Results Prenatal risk factors that have been widely investigated with regards to offspring internalizing and externalizing problems encompass health-related risk factors, including maternal overweight/obesity, substance use/abuse, environmental toxicant exposure, maternal infection/inflammation, as well as psychosocial risk factors, including intimate partner violence, and anxiety/depression. Collectively, both epidemiological and experimental studies support the adverse associations between these prenatal factors and increased risk of emotional/behavioral problem development during childhood and beyond. Potential mechanisms of action underlying these associations include hormonal and immune system alterations. Implications include prenatal education, screening, and intervention strategies.

Conclusions Prenatal risk factors are associated with a constellation of offspring internalizing and externalizing problems. Identifying these risk factors and understanding potential mechanisms will help to develop effective, evidence-based prevention, and intervention strategies.

Keywords Externalizing · Internalizing · Obstetrical · Pregnancy · Prenatal risk factors

Introduction

Childhood behavioral and emotional problems are associated with increased risk for a wide spectrum of later adverse outcomes during adolescence and adulthood [1–6]. Indeed, the Global Burden of Disease study from 2010 estimated that behavioral disorders in childhood accounted for nearly 6 million disability-adjusted life years [7], rendering childhood behavioral problems an increasingly critical public health concern and major societal issue. While much literature has focused on early childhood risk factors for internalizing and externalizing behavior, fewer studies have explored the potential effects of prenatal risk factors on behavioral problems [8]. Understanding this phenomenon has the potential to facilitate recognition, prevention, and mitigation of prenatal risk factors-related childhood behavioral problems, as well as the associated long-lasting negative health consequences. The current literature review aims to examine empirical evidence on the association between common prenatal risk factors and childhood internalizing/externalizing

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behavior, as well as provide a synthesis of the selected studies. Given our comprehensive examination of seven prenatal risk factors, we chose to perform an integrative literature review to allow for the inclusion and simultaneous analysis of diverse research methodologies, both experimental and non-experimental in nature, to provide a broad, all-inclusive overview of available evidence. First, we will provide an overview of child behavioral problems, focusing on internalizing and externalizing behaviors, followed by an introduction of prenatal risk factors significantly associated with those behavioral problems. We will then discuss the link between those factors with internalizing and/or externalizing disorders across the lifespan, with an emphasis on childhood and adolescence. We will also discuss the potential mechanisms underlying those associations. Finally, we will discuss implications of current findings on prevention and intervention strategies.

Childhood behavioral problems

Internalizing and externalizing behaviors are well established and widely used behavioral classifications within the field of child and adolescent psychology [9]. Internalizing problems refer to inwardly focused negative behaviors such as anxiety, depression, and somatic symptoms [10], while externalizing problems refer to outwardly focused negative behaviors such as hyperactivity, aggression, disruptive conduct, and substance use [11, 12]. However, this distinction is not clearly delineated. In fact, there exist high rates of systematic comorbidity between internalizing and externalizing problems [13]. Despite the high degree of overlap, these groupings of behavioral, emotional, and social problems remain highly valuable in guiding research, clinical practices, and policy.

Demonstration of internalizing and/or externalizing behaviors during childhood are predictive of later negative adolescent and adult behavioral, emotional, cognitive, and physical health outcomes, including increased risk for aggression and violence [2, 14], substance abuse [5], depression [3], anxiety disorders [15], lowered academic competence [1], and increased long-term mortality risk in adulthood [16]. Given these profoundly enduring outcomes, research to investigate correlates and early risk factors for childhood internalizing and externalizing behavior is critically important, impacting prevention and intervention approaches for a wide array of negative health consequences.

Prenatal risk factors

For the purposes of this paper, prenatal risk factors will be operationally defined as any condition or exposure during pregnancy that increases fetal susceptibility for internalizing and externalizing behavior. The literature search revealed that two primary groups of prenatal risk factors were significantly associated with childhood internalizing and externalizing behavior: health-related risk factors and psychosocial risk factors. Health-related factors include maternal overweight/obesity, substance use/abuse, environmental toxicant exposure, and maternal infection/inflammation, while psychosocial factors include intimate partner violence and maternal depression and anxiety (Fig. 1).

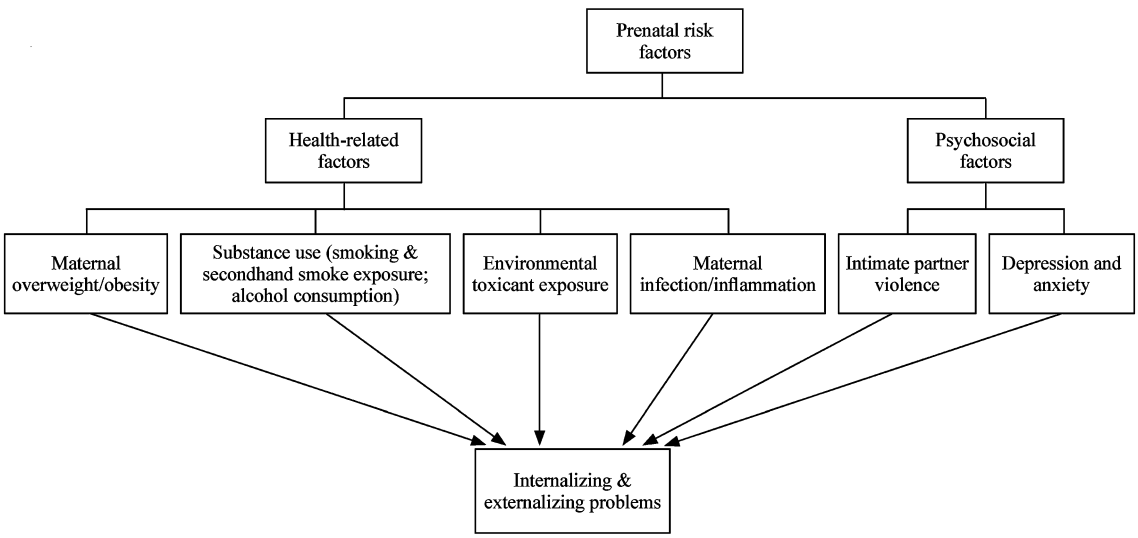

Fig. 1 Prenatal risk factors for internalizing and externalizing problems

The link between prenatal risk factors and childhood internalizing/externalizing behavior

Health-related factors

Maternal overweight/obesity

Maternal overweight/obesity is one of the most common pregnancy complications in the developed world [17]. High maternal pre-pregnancy body mass index (BMI) poses significant risk to the development of offspring behavioral disorders, with considerable evidence for attention-deficit hyperactivity disorder (ADHD) in both human and animal studies. Research from human studies indicated the trend of a higher risk for ADHD in offspring whose mothers had a pre-pregnancy BMI of ≥ 25 kg/m^2. Notably, Rodriguez et al. found a dose-dependent increase in ADHD symptomology as BMI increased from overweight to obese, and when compared to mothers who had normal weight, obese mothers had a twofold increased risk of having a child with ADHD [18]. A recent UK cohort replicated these findings, demonstrating that prenatal maternal very severe obesity is a strongly significant predictor of ADHD symptomology [19]. This association remained even after adjusting for all major confounders, including demographic factors, other prenatal risk factors, and maternal psychological wellbeing. However, when familial confounders, including genetics and shared environment, were taken into account, this association was lost [20]. Another study found that while children of white obese women had increased risk for ADHD symptoms, the same relationship did not hold true for offspring of black obese women [21]. Taken together, these results indicate the need for future research to elucidate the role of a broader range of potential confounders, including but not excluded to racial differences and familial factors.

Animal models of high maternal pre-pregnancy BMI, induced by high fat diet (HFD) consumption, provide support for human epidemiologic data linking maternal overweight/obesity with ADHD. Mouse models of obesity showed that maternal obesity during gestation alone was enough to increase hyperactivity in male offspring performing open-field tests, and decrease sociability (a primary characteristic of ADHD) in female offspring performing chamber social interaction tests [22]. These results are in accordance with those of a previous study, which found increased hyperactivity in adult offspring of obese mice evaluated in open-field tests, light/dark boxes, and novel home cage tests [23].

While there exists substantial evidence for the association between high maternal pre-pregnancy BMI and externalizing behaviors, the association with internalizing behaviors, on the other hand, exhibits mixed results. A large Swedish cohort ($n = 1714$) found that maternal pre-pregnancy overweight and obesity were associated with a teacher-reported twofold increased risk for difficulty with emotional regulation [24]. An Australian cohort ($n = 2785$) similarly found that increased maternal pre-pregnancy BMI was significantly associated with internalizing behavior [25]. The elevated risk for internalizing behavior first emerged at age 8 and increased through age 17. In contrast, a recent US longitudinal study ($n = 2952$) found no significant associations between maternal pre-pregnancy BMI and internalizing problems [26].

Animal research of overweight and obesity shows more consistent results. Rodent models demonstrated increased anxiety in offspring of obese mice in open-field tests [22] and elevated plus mazes [27]. Strikingly, even grandmaternal exposure to HFD exacerbated anxiety- and depression-like phenotypes in the grand-progeny female adult offspring, suggesting the enduring, intergenerational effects of obesity [28]. Likewise, non-human primate models also demonstrated increased anxiety-like behavior in female offspring of obese mothers in response to threatening novel objects compared to controls [29]. The robust results exhibited by animal studies compared to the mixed results by human studies point to the possibility that significant confounders mediate the obesity–internalizing behavior relationship, as well to the importance of future studies to adjust for these confounders.

Substance use

Smoking and secondhand smoke exposure Pregnancy is a critical period in which tobacco exposure may impact fetal development. Maternal smoking during pregnancy (MSDP) has been associated with offspring emotional and behavioral problems [6], with this link studied widely across the lifespan in numerous epidemiological studies. In childhood, an Australian longitudinal cohort study ($n = 7555$ families) utilizing multi-informant data from parents, teachers, and children found a robust relationship between MSDP and level of externalizing symptomology, including hyperactivity, difficulty with peers, and difficulty with behavior [30]. In adolescence, MSDP has been associated with rule-breaking and aggressive behavior [31], as well as hyperactive/impulsive ADHD [32], and increased risk for persisting and increasing externalizing symptom trajectory [33]. While powerful genetic and environmental factors contribute to disorders like ADHD, rendering it difficult to isolate MSDP as an independent risk factor for offspring ADHD, the consistency of results of several carefully controlled studies suggest that maternal smoking during the prenatal period acts as a strong predictor of attention deficits and hyperactive behavior. In fact, a study investigating a large, population-based sample of Dutch twin children ($n = 15{,}228$ pairs) observed a direct causal effect of MSDP on externalizing behavior in children at age 3, with mothers' smoking cessation prior to conception associated with less overall externalizing prob-

lems, including overactive, aggressive, and oppositional behavior [34]. The effects of MSDP on externalizing behavior are strikingly enduring, persisting also into adulthood. A prospective longitudinal investigation of middle-aged adults ($n=3433$) linked MSDP to elevated levels of antisocial behavior as well as violent and non-violent outcomes, with a pack-a-day increase in MSDP more than doubling the odds of an adult violent offense [35], underscoring the lasting adverse effects of smoking during pregnancy on offspring.

Evidence from animal models, primarily rodents, has similarly demonstrated the adverse consequences of prenatal nicotine, the major psychoactive ingredient in tobacco smoke, on offspring externalizing behavior, with most research conducted on ADHD. Focusing on hyperactivity as a measure of ADHD-like behavior, several studies show that prenatal nicotine exposure is associated with offspring impulsivity and elevated locomotor activity [36–38]. However, apart from ADHD, few other forms of externalizing behavior have been investigated with regards to prenatal nicotine exposure, thereby highlighting the need for future studies to employ animal models to understand a broader scope of externalizing behaviors.

While the literature demonstrates consistent results between MSDP and externalizing behavior, those examining the relationship between MSDP and internalizing behaviors show more mixed results, as well as weaker associations. For example, while the Norwegian Mother and Child Cohort Study reported that maternal smoking during early pregnancy shared a dose–response relationship with increased anxiety and depressive behaviors in children at 18 months and 3 years-of-age [39], The Netherlands Twin Register Study, failed to observe an association between MSDP and offspring anxiety or depression at 3 years-of-age [34]. These mixed results for MSDP-associated internalizing behavior extend into adolescence and adulthood as well [40–43]. In contrast to human population studies, experimental animal studies examining the association between MSDP and internalizing behavior, albeit limited, demonstrate a slightly stronger association with prenatal nicotine exposure inducing depression and anxiety-like behavior in offspring rats, with female rats demonstrating greater susceptibility [44–46]. Several possible explanations have been posited for the weaker association between MSDP and internalizing behavior than with externalizing behavior in human studies, including difficulty for adults to accurately perceive internalizing symptomology in young children [30] and the expression of internalizing behavior through "masked" symptoms like aggression in young children [47].

Compared with MSDP, evidence regarding the relationship between maternal passive smoking, or secondhand smoke exposure (SHS) during pregnancy is scarce; however, existing literature shows a robust relationship between prenatal SHS exposure and offspring externalizing behavior, with a high level of consistency demonstrated across countries. Epidemiological studies in China [48, 49], Japan [50], and the United States [36] have all reported a link between prenatal SHS exposure and hyperactivity. These results show that even indirect exposure through secondhand smoke may have adverse consequences on the development of offspring behavioral problems, further reinforcing the need for preventative efforts and continued education on the health hazards of tobacco use, especially with pregnancy as a period of vulnerability.

Alcohol consumption During pregnancy, women are uniformly advised by physicians and other healthcare providers against alcohol consumption; however, the discussion on whether a "safe" level of alcohol may be consumed during pregnancy continues, and is especially relevant in light of recent Centers for Disease Control and Prevention's statistics that one in ten pregnant women in the United States reported alcohol use [51]. Studies examining the effects of low-level alcohol consumption in relation to behavioral problems have found mixed results. A Japanese cohort study ($n=1933$) found that even low prenatal alcohol exposure (PAE) exposure levels (1–4 times per month or less) were associated with children's internalizing problems, as well as overall behavior problems [52]. Day et al. found that these results extend into young adulthood, with all levels of PAE exerting significant effects on internalizing and/or externalizing behavior at each trimester across pregnancy. In fact, the study reported that binge drinking was not a better predictor of adverse behavioral outcomes compared to low/moderate exposure levels [53]. These results remained consistent even after taking into account current offspring substance use, demonstrating the likely permanency of even low/moderate PAE. In contrast, a Danish cohort study observed no associations between low/moderate PAE (an accumulated 0–90 drinks throughout pregnancy) and externalizing and internalizing scores at 7 years-of-age [54]. Strikingly, an earlier Australian cohort ($n=2370$) reported that children of mothers who were light to moderate drinkers during pregnancy (2–10 standard drinks per week) actually exhibited clinically meaningful reduced risk for internalizing, externalizing, and total behavioral problems compared to children of non-drinkers across 14-years-of-age [55].

While the effects of low-to-moderate PAE does not exhibit clear patterns, those of heavier alcohol consumption practices demonstrate more consistent results, especially with externalizing behavior. Using both parent and teacher reports, the Avon Longitudinal Study of Parents and Children found that even episodic binge drinking patterns (≥ 4 drinks in a day) are associated with higher levels of hyperactivity and inattention problems in 11-year-old children, an effect that was not contingent upon daily drinking during pregnancy [56]. Pagnin et al. similarly reported that binge

drinking during pregnancy was associated with a fivefold increased risk for ADHD in offspring at 12-years-of-age [57]. Furthermore, a meta-analysis estimated the prevalence of "disturbance of activity and attention" in offspring with PAE to range from 23.6 to 78.4%, and the prevalence of conduct disorder to even higher percentages of 77.9–97.4% [58]. The detrimental effects of heavy alcohol usage extend well beyond childhood, exerting long-term effects on legal difficulties even in young adulthood [59]. These studies demonstrate the enduring, pervasive effects of heavy PAE, affecting offspring behavioral functioning throughout the life span.

However, several complexities continue to surround human studies of PAE, including stigma, potential underreporting of alcohol consumption during pregnancy [60, 61], varying thresholds of low, moderate, and heavy PAE from study to study [62], and pattern/timing of alcohol exposure during fetal development [63]. These complexities make the comprehensive assessment of the effects of PAE on adverse behavioral development challenging; however, substantial evidence from human studies has indicated that there is perhaps no safe level of maternal alcohol consumption during pregnancy.

Maternal infection/inflammation

Infections are common events during pregnancy, affecting up to nearly 60% of pregnant women [64]. Increasing evidence suggests that maternal exposure to infection during critical periods of prenatal development is associated with increased risk of offspring internalizing and externalizing problems, rendering the high prevalence of maternal infection highly concerning. Much epidemiological literature utilizing prospective, longitudinal cohort designs have linked prenatal maternal infection/immune activation to internalizing behavior in offspring, with a particular focus on depressive and anxious symptomology. This relationship has been well documented across the life course. In childhood, Giollabhui et al. found that maternal inflammation during pregnancy predicts more severe offspring internalizing symptoms, with especially marked effects noted in female offspring [65]. During adolescence, Murphy et al. found that maternal infection specifically during the second trimester was significantly associated with offspring depression at ages 15–17 [66]. Notably, a nationwide Danish cohort found that the risk of mental disorder in both childhood and adolescence increased in a dose–response relationship with the number of maternal infections [67]. The lasting effects of maternal infection endure all the way up to adulthood [68]. Strikingly, maternal infection and inflammation demonstrate strong transgenerational transmission effects, with the second-generation offspring showing enhanced depression-like behavior [69]. Similar behavioral alterations have been found in the animal literature, in which maternal infection is associated with elevated anxiety- and depression-like behaviors with increasing age in mice [70].

Compared to internalizing behavior, the relationship between maternal infection and externalizing behavior is less clear. While several human studies found that maternal infection is associated with lowered impulse control [71] and increased risk for ADHD in offspring [72], other studies found no adverse association between maternal infection during the prenatal period and increased ADHD occurrence in offspring, instead positing that any associations that are found to exist between the two derive largely from unmeasured familial confounding [73, 74]. With regards to experimental research, an animal study utilizing a rodent model found that prenatal inflammation due to *Streptococcus* exposure is significantly associated with hyperactivity in female rats [75]. However, animal studies with regards to externalizing behavior remain limited. These mixed results as well as limited research point to the importance of future research to examine a broader range of infection categories and identify specific time windows of pregnancy during which maternal infection renders offspring more susceptible to externalizing behavior.

Environmental toxicant exposure

There is growing epidemiological evidence demonstrating the associations between prenatal environmental toxicant exposure and offspring emotional/behavior problems. Here, we focus on two major categories of harmful chemicals that have received increasing attention with regards to child and adolescent behavioral problems in recent years. One such major class of environmental toxicants is heavy metals. Mercury is one particularly well-studied heavy metal toxicant, with birth cohorts in several countries including Korea, Canada, and the United States reporting that even low-level prenatal mercury exposure is linked with externalizing behavior [76], especially ADHD [77, 78]. Prenatal lead exposure has also long demonstrated similarly detrimental results on externalizing behavior, with longitudinal [79] and cross-sectional studies [80] finding associations between lead exposure and aggression, attention, antisocial behavior, and juvenile delinquency. Significant gender differences have also been found, with male offspring more susceptible to the effects of lead toxicity than females [79, 81]. While the neurotoxic impact of mercury and lead on behavioral development has been well established, recent studies have also recognized manganese as an emerging neurotoxicant. Longitudinal birth cohort studies examining prenatal manganese exposure in teeth dentine [82], maternal blood [83], and umbilical cord serum [84] have found adverse associations with hyperactivity, attention, neurobehavioral development, and emotional dysfunction.

Besides heavy metals, synthetic organic chemicals are another major class of neurotoxicants whose exposure has

been found to increase externalizing problems in children. Prenatal phthalate exposure has been widely investigated by several birth cohorts, with studies utilizing maternal urine and blood serum samples for toxicant measurement largely suggesting that externalizing problem scores, specifically in the dimensions of aggression [85], conduct problems [86], inattention, and hyperactivity [87], are higher in children whose mothers have greater phthalate exposure [85, 86]. However, prenatal phthalate exposure research on neurodevelopment has primarily been examined in children 1–10 years of age, and the effects of phthalates on adolescent neurodevelopment and behavior are unclear. In one recent study following neurobehavioral development in a 15-year follow-up Taiwanese birth cohort, Huang et al. found that elevated maternal urinary phthalate levels are associated with attention problems, delinquent behavior, aggression, and other externalizing problems in children 8–14 years old [88]. Further research in this age group as well as in adolescents is necessary to confirm these associations. Polybrominated diphenyl ethers (PBDE) are yet another class of harmful chemicals that have raised concerns regarding their impact upon offspring development. Their exposure has been evaluated at various points of development, including prenatal exposure in maternal blood serum [89, 90] and postnatal exposure in breast milk [91], indicating the positive association between PBDE concentration and activity, impulsivity, and attention problems up to 12-years of age. Furthermore, bisphenol A (BPA) studies in both humans and animal models [92–98] have extensively documented the association of prenatal and early postnatal BPA exposure with increased aggression and hyperactivity. Given the ubiquity of these environmental toxins, not only is it important to independently assess safe levels of exposure for a wider spectrum of toxicants, but also to further elucidate the interplay of multiple neurotoxicant co-exposures on the development of behavioral problems. More research assessing the timing of exposure on the severity and prevalence of internalizing and externalizing problems should also be assessed to best inform best maternity leave policies that minimize workplace exposure.

Psychosocial factors

Intimate partner violence

The World Health Organization has declared intimate partner violence (IPV) a global public health concern, estimating that one in three women throughout the world will experience physical and/or sexual violence by a partner or sexual violence by a non-partner [99]. These statistics are especially alarming in lights of the considerable health risks that IPV poses to offspring. However, while much research has focused on IPV exposure during childhood, research on the role of prenatal IPV as a risk factor for behavioral and emotional problems after birth is scarce. Current studies have documented significant associations between prenatal IPV and both internalizing and externalizing behavior across infancy and childhood. Martinez-Torteya et al. found that in utero IPV exposure acts as a strong predictor of offspring externalizing behavior at 12 months of age. They also found associations with internalizing behavior, but this relationship was attenuated after taking into account stress hormone activity patterns [100]. At 24 months, McFarlane et al. reported that children residing with mothers exposed to IPV during pregnancy had greater problems with internalizing problems, specifically anxiety and depression [101]. At 42 months, Flach et al. found children exhibited externalizing problems, including conduct problems, if their mothers were exposed to antenatal IPV [102]. The long-term behavioral outcomes of prenatal IPV exposure have also been evaluated using prospective, longitudinal design. The study found that IPV exposure during pregnancy predicted child-reported internalizing and externalizing problems, as well as mother-rated externalizing problems, at age 10 [103]. A meta-analysis involving adolescents up to 16 years of age, however, did not find consistent associations between prenatal IPV exposure and adolescent internalizing and/or externalizing behavior [104], indicating that enduring influences may only be maintained up to childhood. Given the dearth of research in this area, future research should aim to rule out confounders that may mediate the associations, including genetic, familial, and environmental influences, as well as evaluate the frequencies, severity, and context of violence.

Maternal psychopathology—anxiety and depression

Pregnancy is a time of increased vulnerability for psychiatric disorders, with anxiety and depression being two of the most common psychopathologies experienced by expecting mothers [105]. Maternal anxiety and depression during pregnancy are known risk factors for internalizing and externalizing behavior in offspring, with several longitudinal cohort studies from multiple countries providing extensive evidence of their associations across the lifespan. During early childhood, a Canadian birth cohort study found that having a mother with either subclinical or high depressive symptoms trajectory across pregnancy is associated with an increased risk for hyperactivity, inattention, physical aggression, emotional/anxiety disorder, and separation anxiety symptoms in offspring at 3 years-of-age [106]. These associations shared a dose–response relationship, with the proportion of children with internalizing and/or externalizing behavior highest for those whose mothers presented with the most persistent and severe depressive symptoms. Similarly, data from an earlier Australian pregnancy cohort found consistent results that 4-year-old children whose mothers experienced either subclinical or high depressive symptoms had at least two-times

elevated risk for emotional–behavioral difficulties compared to their unaffected counterparts [107]. In middle childhood, the results found by a French longitudinal cohort continued to be in agreement, with prenatal depression linked to heightened depressive and antisocial behavior symptoms [108]. These effects have also been observed in many adolescent longitudinal cohorts. Two Finish cohorts reported associations between prenatal depression and emotional/behavioral problems; however, while one determined that mother's depressed mood in the first trimester best predicted children's externalizing problems at age 12 [109], another found symptom pattern and trajectory, rather than timing of depressive symptoms, better explain higher levels of adolescent internalizing and externalizing behavior [110]. When participants were in adulthood, an Australian-based pre-birth cohort reported the long-term effects of prenatal psychopathology on behavioral problems at the 21-year follow-up, with comorbid depressive, anxious, and stress symptoms during pregnancy predicting mental health outcomes in adult offspring [111].

Results consistent with those found in human studies have also been documented in animal research. Prenatal exposure to selective serotonin reuptake inhibitors, a staple pharmacological treatment for women experiencing depression, elicits a variety of lasting emotional and behavioral abnormalities in rodents, including increased adult behavioral despair as indicated by immobility on the forced swim test [112, 113], anxiety-like behavior as shown by reduced exploratory behavior in the elevated plus maze [114] and open-field test [115, 116], and aggression in the social exploration [117] and territorial behavior [118] tests. Together, findings from human and experimental studies suggest offspring susceptibility to maternal emotional problems and early life antidepressant exposure. Given the detrimental consequences of fetal insult resulting from prenatal anxiety and depression, two highly prevalent risk factors during pregnancy, future research investigating this relationship should take into account more comprehensive measures, including symptom severity, recurrence and pattern of symptoms, symptom chronicity, and exposure to treatment/medication.

Potential mechanisms of action

While the specific mechanisms of action through which the health-related and psychosocial prenatal risk factors presented above act on offspring internalizing and externalizing problems are not well understood, several potential mechanisms have been posited. One widely investigated biological hypothesis involves hormonal mechanisms. In particular, the associations between several prenatal risk factors and offspring emotional/behavioral problems have been proposed to be mediated by glucocorticoids [119, 120], the central hormone of the hypothalamic–pituitary–adrenal (HPA) axis. Prenatal drug exposure, including tobacco and alcohol, has been found to attenuate cortisol reactivity in adolescents, an HPA axis disruption that manifested as risky health behaviors, aggression, and other externalizing behaviors [121]. Furthermore, the epigenetic modulation of the human glucocorticoid receptor gene, *NR3C1*, in offspring has been widely implicated in the development of internalizing and/or externalizing behaviors with regards to intimate partner violence [122], prenatal depression [123], and anxiety [124, 125], with higher methylation levels dysregulating stress responses and increasing vulnerability to emotional and behavioral problems. These modulations have been studied in several physiological contexts, including blood, placenta, and saliva. Apart from glucocorticoids, other hormones have also been found to mediate the relationship between health-related factors and offspring behavioral problems. For example, prenatal BPA exposure has been linked to disruptions in the fetal endocrine system, specifically the thyroid–adipokine axis. Previous results of several studies have suggested multiple mechanisms, including BPA-induced disruption of thyroid hormone receptors [126], interference of thyroid hormone functions by inhibiting synthesis [126], and alteration of thyrotropin-releasing hormone that inhibited iodide uptake by the sodium iodide symporter [127]. Further research is necessary to take into account potential social and environmental confounders given the length of time between prenatal exposure and the onset of behavioral problems [128], as well as examine the modifiability of these epigenetic mechanisms as a way of mitigating their adverse effects [123].

Alterations to the immune system are another biological mechanism that may mediate susceptibility to these conditions. With regards to maternal infection, infectious agents have been proposed to affect the developing fetus during the prenatal period through activation of the immune response [129]. With regards to pre-pregnancy weight, obesity has been found to systemically activate the maternal immune system, producing increased fetal brain inflammation via elevated cytokine expression within the offspring brain at birth. This thereby heightens susceptibility to mental health disorders [130, 131]. With regards to maternal infection, several studies utilizing animal models have found that maternal infection during pregnancy is associated with behavioral phenotypes in mice offspring that reflect depressive symptomology in humans [132, 133]. Specifically, maternal infection has been found to lead to the upregulation of pro- and anti-inflammatory cytokines, which are significantly implicated in the development of depression [134]. Many cytokines have been investigated to elucidate their specific roles within the pathway linking maternal infection with offspring emotional and behavioral aberrations, with several lines of experimental research indicating interleukin-6 as a key mediator [135, 136]. However, the exact mechanisms of

cytokine augmentation as well as cytokine-specific effects are still not clearly understood. With regards to maternal anxiety and depression during pregnancy, elevated maternal inflammatory cytokines levels have been found to mediate the effects of psychological distress on infant internalizing behavior, particularly sadness [137]. However, while other studies to date have also observed the association between maternal psychopathology with altered cytokine levels during pregnancy [138–140], few have definitively found the link between inflammation levels and offspring behavioral outcomes, exposing the need for future research to elucidate this relationship. Inflammatory cytokines have also been implicated in prenatal tobacco and alcohol exposure [141, 142], environmental toxins [143], and intimate partner violence [144]; however, more research must be performed to establish causal pathways between these risk factors, inflammatory cytokines, and offspring outcomes.

Implications

Pregnancy is a time during which women re-assess their health, behavioral, and lifestyle choices, thus making it a unique window of opportunity. Understanding the broad spectrum of internalizing and externalizing outcomes that prenatal risk factors pose to offspring will not only aid clinicians, researchers, and policy-makers in integrating successful evidence-based prevention and intervention strategies into a regular part of obstetric care, but also better help expecting mothers manage health for both themselves and their offspring during a time when they are particularly receptive to care. The prenatal risk factors presented in this paper and their key clinical implications are summarized in Table 1.

Health-related implications

With regards to many health-related prenatal risk factors, pregnancy represents a window of opportunity for expecting women to re-evaluate their lifestyles and health behaviors. Thus, elucidating the associations between these risk factors and emotional/behavioral problems is critical in both clinical and public health settings for developing successful prevention and intervention methods during a unique time frame when women regularly interact with healthcare professionals.

Concerning maternal overweight and obesity, health care providers should promote prenatal care for expecting mothers to receive standardized metabolic tests and weight-management interventions [145–147]. Furthermore, obstetricians should regularly promote a combination of dietary [148], physical activity [149], and behavioral modifications specific for weight management during pregnancy. Apart from generalized guidelines, physicians should also refer expecting mothers who are overweight or obese to dieticians for nutritional counseling and other tailored prenatal weight-management methods that take into account factors such as socioeconomic status [150] and culture [151, 152]. However, while nutritional strategies have generally found to be useful in preventing maternal overweight/obesity, studies have also found insufficient evidence regarding the efficacy of lifestyle interventions on birth outcomes [153], therefore underscoring the need for further research to develop effective strategies.

Concerning substance use during pregnancy, including smoking and alcohol consumption, healthcare providers should educate parents on the negative consequences of substance use on offspring [154], as well as support pre-pregnancy quitting. Strategies for pre-pregnancy quitting include widely displaying media messages that emphasize the link between prenatal smoke/alcohol exposure and offspring emotional/behavioral health, and engaging clinicians, such as primary care physicians, to promote cessation prior to pregnancy [155]. They should furthermore universally screen for tobacco/alcohol use at initial prenatal visits, monitor usage status during each subsequent visit, and support continued cessation throughout the duration of the pregnancy to prevent relapse. Strategies for cessation during pregnancy must be cognizant of individuals who may be resistant to educational interventions and quitting. Interventions, including behavioral [156] and psychosocial [157, 158] cessation counseling sessions, as well as pharmacotherapy interventions [159, 160], have all shown to be effective in smoking cessation. Finally, arranging for follow-up visits to monitor progress is critical for continued cessation during the intervention process.

Concerning environmental toxicant exposure, education on proper avoidance or mitigation of effects of hazards during pregnancy is integral to both maternal and fetal health. Currently, healthcare providers are not routinely trained in environmental health, and environmental health screening is not incorporated as part of standard practice. Inclusion of such training and development of standardized screening tools is a necessity for risk reduction during pregnancy. Healthcare providers should include reproductive environmental health as a routine part of obstetric care, including the collection of patients' environmental health exposure histories [161], as well as conduct screenings of ubiquitous environmental toxins and assess the risk of environmental toxin exposure in the home and workplace. Furthermore, obstetricians should provide dietary advice, including educating women that healthful nutrition may act as protective factors modulating the toxicity of environmental pollutants [145, 162]. They should furthermore advise women to avoid diets that may contain significant amounts of environmental toxins [163]. Apart from dietary advice, expecting mothers should also be encouraged to consult Teratology Information Services, a platform focused on advising women planning

Table 1 Prenatal risk factors and their key clinical implications for healthcare providers

Variables	Prenatal risk factors	Key clinical implications
Health-related factors	Maternal overweight/obesity	Promote prenatal care for expecting mothers to receive standardized metabolic tests and weight-management interventions [115] Emphasize guidelines for expecting mothers in dietary, physical activity, and behavioral management [116, 117] Refer overweight/obese expecting mothers to nutritional counseling [142]
	Substance use/abuse (smoking and secondhand smoke exposure/alcohol consumption)	Educate parents on the negative consequences of substance use on offspring [122] Promote pre-pregnancy quitting through educational means in clinical and everyday settings [123] Screen prospective and expecting mothers for tobacco and alcohol use at initial prenatal visits, monitor status at each visit, and support feasible strategies for continued cessation, including behavioral and psychosocial interventions, smoke/alcohol cessation counseling, and pharmacotherapy [123, 124, 126, 143]
	Environmental toxic exposure	Educate expecting mothers on risks of environmental health hazards (e.g., lead exposure) and appropriate prevention methods Collect environmental health exposure histories as routine part of obstetric care [129] Conduct screenings of ubiquitous environmental toxins and assess environmental toxicity risk in the home [129] Provide dietary advice of foods that may act as risk or protective factors for environmental toxin exposure [131, 132] Encourage expecting mothers to consult Teratology Information Services [133] and Pediatric Environmental Health Specialty Units [145]
	Maternal infection/inflammation	Improve immunization rates for pregnant women and women of childbearing age Inform patients of increased complication and hospitalization risk due to infection during pregnancy Test pregnant women for common infectious agents as a part of standard prenatal care [146] In the case of infection, discuss the pros and cons of anti-viral drugs with patients Screen children for prenatal exposure to maternal infection
Psychosocial factors	Intimate partner violence (IPV)	Inquire about IPV exposure throughout multiple points throughout prenatal care to increase disclosure rates Offer ongoing support through counseling, home visits, and mentoring [96, 138]
	Depression and anxiety	Screen expecting mothers for depression and anxiety throughout prenatal care Referral for those who exhibit symptoms of emotional problems for further evaluation Follow-up with treatment and therapy, including cognitive behavioral therapy and nutritional medicine [140, 144]

pregnancy, pregnant women, breast-feeding women, and their families on the reproductive safety or risk of prenatal exposures [146, 164], as well as the Pediatric Environmental Health Specialty Units, a nationwide network of specialists who provide consultation and training to health care providers and the general public [165].

Concerning maternal infection/inflammation, public health campaigns and community health efforts should focus on improving immunization rates for pregnant women and women of childbearing age. For example, although the Advisory Committee on Immunization Practices recommends the influenza vaccine for women who are pregnant during the influenza season, only 53.6% of pregnant women reported having received the vaccine before or during pregnancy during the 2016–17 influenza season [166]. To promote vaccination uptake, clinicians providing care for pregnant women may inform patients of the increased risk for complications and hospitalizations of infection during pregnancy, as well as the lasting implications upon offspring emotional and behavioral development. Furthermore, obstetricians may consider testing pregnant women for common infectious agents, including hepatitis B, human immunodeficiency virus, rubella, gonorrhea, and chlamydia as a standard part of prenatal care [167]. In the case of infection, the benefits of anti-viral drugs may be discussed with the patient, taking into consideration the type of drug, the timing of exposure, and the gestational period. Following birth, pediatricians should screen children for prenatal exposure to maternal infections for early identification of potential internalizing and externalizing behavior.

Prevention and intervention strategies for all previously discussed health-related factors should involve mobilization of not only the individual, but also community and governmental efforts. Policies and political action, such as

improved maternal access to food in underserved communities [168], improved healthcare coverage benefits for smoking and alcohol cessation services during pregnancy [169], governmental regulation of workplace chemicals known to cause reproductive harm, and policies that limit permissible exposure in expecting women [161], should supplement clinical approaches for maximum effectiveness. These broad-scaled policy changes would complement individualized obstetric care by helping women generate their own capacity for change.

Psychosocial implications

The stigma surrounding IPV and mental health coupled with their deleterious effects warrant rigorous, active detection, and monitoring of psychosocial risk factors during pregnancy. With regards to IPV, inquiries should be made as a universal part of obstetric care (during the initial visit and at least once per trimester) [170] to increase the opportunity for disclosure. Indeed, routine and repeated screening for IPV during the prenatal period has been shown to increase disclosure rates among women exposed to IPV during pregnancy [101, 171]. When screening results indicate IPV, healthcare providers should offer ongoing support, review available prevention and intervention options including counseling, home visits, and mentoring support, and provide referrals to support services for abused women.

With regards to anxiety and depression, screenings for the detection and treatment of maternal psychopathology should be a core part of women's obstetric health visits. Recent evidence suggests that simply screening pregnant women, even without additional treatment-related support, increased rates of treatment seeking and reduced the prevalence of depression [172]. Those who screen positively should promptly be referred for consultation for mental health care, including further evaluation, a formal diagnosis, and treatment, including cognitive behavioral therapy [173] and nutritional medicine [174]. These services should be provided by collaborative, multidisciplinary care teams of clinicians, therapists, and social workers to best mitigate the deleterious effects of maternal psychopathology on offspring outcomes.

Conclusions

Mounting evidence shows that prenatal health and psychosocial risk factors predispose offspring to negative outcomes, including childhood internalizing/externalizing problems. These risk factors may modify the in utero environment, leading to stress and immune system alterations that shape offspring emotional/behavioral outcomes in childhood and beyond. Understanding these risk factors are significant given that the prenatal period is an important window of time for fetal neurobehavioral development, as well as childhood internalizing/externalizing problems are risk factors for later adverse physical and mental health outcomes. Thus, developing evidence-based prevention/intervention strategies for expecting mothers and clinicians is critical to reducing negative behavioral outcomes in future generations.

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Compliance with ethical standards

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