Review

Biological Psychiatry

Maternal Mental Health and Offspring Brain Development: An Umbrella Review of Prenatal Interventions

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ABSTRACT

The idea that risk for psychiatric disorders may be transmitted intergenerationally via prenatal programming places interest in the prenatal period as a critical moment during which intervention efforts may have a strong impact, yet studies testing whether prenatal interventions also protect offspring are limited. The present umbrella review of systematic reviews and meta-analyses (SRMAs) of randomized controlled trials aimed to synthesize the available evidence and highlight promising avenues for intervention. Overall, the literature provides mixed and limited evidence in support of prenatal interventions. Thirty SRMAs were included. Of the 23 SRMAs that reported on prenatal depression interventions, 16 found a significant effect (average standard mean difference = −0.45, SD = 0.25). Similarly, 13 of the 20 SRMAs that reported on anxiety outcomes documented significant reductions (average standard mean difference = −0.76, SD = 0.95 or −0.53/0.53 excluding one outlier). Only 4 SRMAs reported child outcomes, and only 2 (of 10) analyses showed significant effects of prenatal interventions (massage and telephone support on neonatal resuscitation [relative risk = 0.43] and neonatal intensive care unit admissions [relative risk = 0.91]). Notably missing, perhaps due to our strict inclusion criteria (inclusion of randomized controlled trials only), were interventions focusing on key facets of prenatal health (e.g., whole diet, sleep). Structural interventions (housing, access to health care, economic security) were not included, although initial success has been documented in non-SRMAs. Most notably, none of the SRMAs focused on offspring mental health or neurodevelopmental outcomes. Given the possibility that interventions deployed in this period will positively impact the next generation, randomized trials that focus on offspring outcomes are urgently needed.

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The recent explosion of studies on the Developmental Origins of Health and Disease has led to an increased realization of how plastic—and thus susceptible—the brain is early in development. Embedded in the idea that psychopathology risk may start in the perinatal period is the hope that interventions during this time could prevent or counteract the effects of perinatal risks for offspring's future psychopathology. For this promise to be fulfilled, Developmental Origins of Health and Disease studies will need to move beyond identifying risks to developing and testing interventions. Interventions aimed at treating maternal mental health problems and distress in the prenatal period are urgently needed for several reasons. A growing body of work shows that prenatal maternal distress is associated with atypical offspring neurodevelopment and increased risk for psychiatric disorders. Further, the prenatal period is a time in which a significant number of persons develop or have a recurrence of mental health problems. In fact, psychiatric disorders are among the most common pregnancy morbidities (1). Depression and anxiety disorders are the top two, with 10% to 20% of pregnant people expected to experience some form of these disorders (1,2). However, research on prenatal interventions aimed at improving maternal health and optimizing offspring brain development has lagged, limiting the clinical and public health impact of this work. Existing research is deficient in its lack of inclusion of individuals from ethnically and racially minoritized backgrounds and may, crucially, not support solutions tailored to the needs of populations with the highest rates of mental health problems in pregnancy and the most barriers to care. As interactions with health care providers increase during pregnancy, interventions at this stage may help decrease inequities in maternal mental health and offspring development.

In this review, we aim to provide an overview of the state of the science on prenatal interventions and their potential intergenerational impacts on offspring, for which we conduct an umbrella review of systematic reviews and meta-analyses (SRMAs) of randomized controlled trials (RCTs) of prenatal interventions on mental health or emotional problems in the prenatal period. We conclude our review highlighting newer intervention areas and studies that were not included in the umbrella review and are in need of further study.

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METHODS

For the umbrella review, PubMed, Embase, and Cochrane were searched for articles published from January 1, 1994, to December 18, 2022. The search strategy and inclusion and exclusion criteria are detailed in the Supplement, but briefly, peer-reviewed studies were included in the umbrella review if they met the following criteria: 1) consisted of SRMAs of RCTs, 2) examined the impact of interventions on prenatal emotional problems (and thus include interventions and outcomes during pregnancy—inclusive of delivery), and 3) were in English. Given existing reviews (3–5) and space limitations, pharmacological interventions and interventions focused on decreasing or preventing tobacco, alcohol, and other substance use were excluded. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Although our focus is on the intergenerational ramifications of prenatal interventions, we included studies even if they did not include offspring outcomes, aiming to provide a broader view of where the field is rather than just focusing on an extremely limited number of studies (n = 7).

The search strategy and inclusion and exclusion criteria were decided and registered before commencing the review (International Prospective Register of Systematic Reviews CRD42022384003). Two reviewers independently conducted screenings and full-text reviews. Extraction was completed with a predetermined extraction form.

RESULTS

Description of Included Studies

After screening and full-text review, 30 SRMAs met the criteria and were included in the current study. See Figure S1 and the Supplement for details; briefly, non-RCTs resulted in 31 exclusions. Noticeably, lack of clarity about the time frame of the intervention (n = 6) or of the outcomes (n = 21) examined contributed to a large number of exclusions, as many studies examined pre- and postnatal populations either jointly or did not provide sufficient details to determine the life stage examined (preconception, prenatal, postnatal).

Of the SRMAs included, 6 examined psychological interventions (e.g., psychotherapy), 5 examined mind-body interventions (MBIs) (e.g., yoga, mindfulness), 4 examined lifestyle interventions (e.g., omega-3 supplementation, physical activity), 11 examined other interventions (e.g., fetal movement counseling, virtual reality during delivery), and 4 reviews examined multiple intervention types. The AMSTAR 2 instrument was used to evaluate the characteristics of the studies, which are detailed in Table S4.

Key Results on Maternal Mental Health Outcomes

Table S2 summarizes the maternal mental health outcomes examined.

Of the 30 SRMAs reviewed, 24 performed at least one meta-analysis of the outcomes of interest, 1 did not identify any study fulfilling inclusion criteria (6), and for 5, outcomes extracted were based either on a single study (4 SRMAs) or on a qualitative appraisal of results (1 SRMA). A total of 48 outcomes were extracted and analyzed for this umbrella review: for 29 of the 30 SRMAs, at least 1 outcome was included [1 SRMA did not identify any eligible study (6)]; for 13 SRMAs, 2 outcomes; and for 6 SRMAs, 3 maternal mental health outcomes during pregnancy were analyzed. Eleven of the 48 outcomes analyzed were based on results from a single study, and 1 SRMA was based on a qualitative evaluation of the studies assessed (7).

Of the 48 maternal mental health outcomes extracted, 23 were related to maternal depression during pregnancy, 20 were related to maternal anxiety, and 5 reported on other mental health conditions (specifically, emotional experiences and stress). Mean differences (when k = 1), standard mean differences (SMDs), or relative risk (RR) were the most used effect size measures. When calculating SMDs, we ensured all effects would reflect the subtraction of the intervention from the comparison group (findings from 3 studies were multiplied by −1). These effects are displayed in Table S2, together with the 95% CIs and p values, when available.

Assuming α = 0.05, 30 of the 48 effect size estimates extracted would be considered statistically significant, that is, suggesting an effect of a prenatal intervention on a prenatal maternal mental health outcome. Half or more of the outcomes examined supported an effect of the intervention examined across different maternal pregnancy outcomes: of the 23 estimates related to the effect of pregnancy interventions on maternal depression, 16 were statistically significant. Of the 20 estimates pertaining to maternal anxiety, 13 were statistically significant, and the same was true for 2 of the 5 estimates related to other maternal mental health conditions.

Based only on SRMA outcomes resulting from meta-analyses that were summarized as SMDs or g effects (29 outcomes); the magnitude of the effects overall ranged from −3.3 to 0.10, with a medium-sized average effect of −0.58 (−0.65 SD). Of these, 16 effect sizes were related to depression with an average/SD of −0.45/0.25, and 12 effect sizes were related to anxiety (average/SD = −0.76/0.95 or −0.53/0.53, excluding 1 outlier). Only one outcome (depression) was summarized as a relative risk (RR = 0.84; 95% CI, 0.74–0.96; p = .010) (8).

In relation to the type of intervention, there were 29 effect sizes summarized as SMD (6 psychological, 5 mindfulness, 4 lifestyle, 5 multiple, and 9 other interventions). Average SMDs ranged from small to medium for psychological (average/SD = −0.23/0.14) and lifestyle (average/SD = −0.39/0.10) interventions and were larger for mindfulness (average/SD = −0.52/0.38), other (average/SD = −0.82/1.07), and multiple (average/SD = −0.80/0.19) interventions. Interestingly, both other and multiple interventions included effects that were above 1 [3 effects and 1 effect, respectively (9–12)]. Without the effects above 1, average SMDs were −0.23 (SD = 0.23) and −0.78 (SD = 0.14) for other and multiple interventions, respectively.

Key Results on Offspring Outcomes

Of the 30 SRMAs reviewed, only 7 examined offspring outcomes. Of these, 3 did not report effect sizes, resulting in 4 studies with a meta-analysis of offspring outcomes. Of the 17 offspring outcomes extracted, 5 examined outcomes related to Apgar score, 4 to birth weight, 3 to preterm birth, 2 to gestational age at birth, 2 to neonatal intensive care unit admission,

and 1 to resuscitation of the newborn. Effect sizes are displayed in Table S3.

Of these 17 outcomes, only 10 reported average outcome effects. Of these 10 summary effects, only 2 were statistically significant. They examined neonatal resuscitation outcomes following a prenatal massage intervention and major neonatal, infant morbidity, and/or admission to neonatal intensive care unit following a prenatal telephone support intervention. Both reported relative risk ratios and low heterogeneity (prenatal massage: RR = 0.43; 95% CI, 0.23–0.79; $p = .0068$; $I^2 = 0\%$; telephone support: RR = 0.91; 95% CI, 0.77–1.08; $p = .03$; $I^2 = 0\%$), yet both meta-analyses were based on only 2 trials, and both met over 10 AMSTAR 2 criteria.

Quality Assessment

We used the AMSTAR 2 instrument to evaluate the quality of the SRMAs included. The 30 SRMAs included fulfilled on average 52.5% (SD = 16; ranging from 18.8% to 81.3%) of 16 criteria examined. Four of the studies included fulfilled 25% or less of the valid criteria (6,8,11,13–15). Few (<34%) of the SRMAs reviewed included a clear statement about the review methods having been established before the SRMA being conducted, explained their selection of the study design (RCT), described the studies included in adequate details, reported on the source of funding for the studies included in the review, or discussed the potential impact of risk of bias in specific studies included (meta-analyses only) (see Table S4).

Key Takeaways From the Umbrella Review

Our review demonstrates that the current body of knowledge is critically limited by few, and often small, inconsistent, and possibly biased studies. Many analyses were characterized by high or unknown heterogeneity, possibly contributing to mixed findings. Our review also found that very few RCTs have examined offspring outcomes, with none of the reviewed SRMAs examining outcomes beyond delivery and birth. Whereas our strict inclusion criteria (only RCTs) could have limited the scope of our analyses, it is noteworthy that many SRMAs of RCTs were excluded due to poorly specified intervention and outcome assessment timelines. By conflating prenatal and postnatal interventions and assessments, a considerable number of studies obfuscate effects specific to the prenatal period, thus limiting our knowledge of prenatal programming effects. Overall, until higher-quality RCTs are conducted, the value of prenatal interventions on maternal and offspring outcomes remains uncertain.

Innovative and Noteworthy Interventions Not Included in the Umbrella Review

We conclude by highlighting particularly innovative or promising interventions, devoting some space to interventions that, although in need of rigorous testing, have shown preliminary support in observational studies or single RCTs and have thus been excluded from our umbrella review.

Psychological Interventions. One notable absence from our search was a 2018 meta-analysis of 25 RCTs focused on prevention [e.g., PREPP (16)] and treatment of prenatal depression. This meta-analysis found some support for protective effects on offspring outcomes, documenting interventions that were related to offspring regulatory abilities but not to cognitive development or socioemotional competence (only 2 studies measured behavioral/emotional problems) (17). Limitations included the high number of women without depression and infant regulatory abilities being measured either very early in development (e.g., Brazelton scale), or via parent report, which may have introduced reporter bias. Intergenerational studies on interventions that have been specifically designed for low-income and racially and ethnically diverse women [e.g., ROSE (18)] are of particular interest.

Mind-Body Interventions. MBIs may be a promising way to increase accessibility and acceptability. Specifically, an MBI can be accessible in alternative delivery formats (e.g., brief, self-paced, app- or internet-based sessions, online or offline recordings) and do not necessarily require the presence of clinicians. Health care systems such as Kaiser Permanente have already incorporated MBI-based mobile-based mental health apps as a part of routine care. However, RCTs are still underway. One large RCT focuses on Black and Latina pregnant persons who are at risk of postpartum depression (due to the presence of prenatal depressive symptoms) and uses a mobile-based MBI to reduce the risk of postpartum depression (19). Another tests the efficacy of a 12-week intervention that involves symptom self-management discussions plus group-based prenatal yoga, examining social connectedness as a moderator, and genome-wide DNA methylation patterns associated with levels of perceived social connectedness (20). This line of research on MBIs for maternal health is the foundation to further examine the impact on offspring outcomes such as brain development, DNA methylation, and eventually preventing intergenerational transmission of mental health problems. While, to our knowledge, no RCTs have examined if MBIs are effective at protecting fetal or infant brain development, a recent observational study found that offspring of pregnant women who were more mindful (naturally, no intervention was deployed) had newborns who exhibited greater arousal (but not greater attention) (21). Again, while preliminary evidence supports that MBI may be an effective tool in the prenatal period, intervention trials that focus on offspring outcomes are needed.

Other Lifestyle Interventions. Dietary interventions focused on specific nutrient supplementation (e.g., the multiple omega-3 studies reviewed here) have largely failed to document significant improvements in prenatal maternal mood. Further, few studies have examined offspring outcomes (22). In response, it has been proposed that whole-diet intervention approaches may be needed, as there could be a number of nutrients and infinite combinations of these necessary to have an effect on prenatal distress and prevent intergenerational transmission (23,24). Furthermore, studies have observed that there are a number of environmental and contextual factors (socioeconomic status, stress, general undernourishment) that can limit or amplify intervention effects (25,26).

One noteworthy example is the Healthy MOMs Healthy Lifestyle Intervention study, an 11-week lifestyle intervention that includes psychoeducation and workshops about pregnancy lifestyle issues, highlighting the importance of a healthy diet and physical activity. This program is community-planned and culturally tailored for Spanish-speaking pregnant Latine people. Although it was originally designed to reduce risk factors for obesity and type 2 diabetes, it reduced depressive symptoms (27), highlighting how holistic interventions can simultaneously improve prenatal mental health and nutrition-related outcomes (28). However, how effective such interventions will prove in preventing offspring's psychiatric risk is yet to be assessed, as this and other interventions have focused on offspring outcomes such as diabetes and obesity.

Interventions have also started to target putative mechanisms (e.g., inflammation) underlying intergenerational transmissions. For example, the Pregnancy Exercise and Nutrition Study in Ireland used a low-glycemic dietary intervention (1 session; psychoeducation) and found that the intervention was related to maternal diets lower in a dietary inflammatory index (29), yet a preliminary study showed that prenatal diets that lowered this index were not related to better offspring outcomes (30). Other studies have documented that in the context of high prenatal inflammation, nutrients like choline may have protective effects on offspring neurodevelopment, but intervention studies have not been carried out (31). Additional interventions include microbiome-targeted interventions, yet trials are currently underway and outcomes to date have not included maternal or offspring mental health (32). Finally, nutritional interventions show preliminary success in altering DNA methylation patterns in offspring, yet the long-term effects on offspring psychiatric risk are to be determined (33).

As shown in the studies reviewed, physical activity in pregnancy may lead to reduced maternal distress. However, studies of offspring outcomes have mostly focused on cognitive and language developmental outcomes, not psychopathology (34,35). Newer interventions have focused on diversifying delivery methods and have documented some success with phone apps and activity trackers (e.g., Fitbit)—yet the main hurdle appears to be in motivating individuals with fairly sedentary lifestyles to increase physical activity in the perinatal period (36,37).

Finally, prenatal maternal sleep health has started to receive more attention as an important facet of prenatal health, with observational studies documenting that poor prenatal maternal sleep health is associated with maternal perinatal depression and externalizing and sleep problems in offspring (38–40). To date, no intervention studies have examined offspring outcomes.

Structural Interventions. Public health structural interventions aim to modify structural factors that impact health to produce better health outcomes (41,42). Certain aspects of one's structural context, like housing, access to health care, and economic security, can critically affect maternal and fetal health and impact offspring neurodevelopment. Studies have focused on improving maternal health care (43,44), housing conditions (45), or supplementing income (46). Some studies have taken an intergenerational focus and addressed how modifying structural factors during pregnancy may improve adverse birth outcomes, like low birth weight (47). Another study examined how prenatal health care was related to a biological process relevant for future offspring development, DNA methylation (48). Less widely studied is the impact of prenatal structural interventions on maternal mental health and infant neurodevelopment.

Several studies have supported positive fetal outcomes following structural interventions involving stable housing, health care access, and economic security during pregnancy (47,49,50). In observational studies, housing instability during pregnancy predicted low birth weight and/or preterm birth, neonatal intensive care unit or stepdown stay, and extended hospitalization (51,52). A case-control study in Brazil focusing on postpartum women found that poor housing conditions were associated with low birth weight (53). Celebrate One in Columbus, Ohio, a maternal and infant intervention program, targeted multiple sectors, including addressing housing needs for mothers, and a decline in infant mortality was observed (54). Future studies need to include randomized designs.

Health care access interventions such as prenatal home visitation by health professionals has received considerable support. Nurse-Family Partnership, the leading community health program for home visiting by nurses for low-income mothers from pregnancy through toddlerhood, reported an impact on adolescent offspring's antisocial behaviors and on substance use as well as improved cognitive-related abilities (i.e., receptive language and math achievement) among 18-year-old adolescents born to mothers with limited resources (55,56). Two RCTs reported reduced low-birth-weight deliveries among women with low incomes (49,57), and 1 RCT found a positive effect on preterm birth (50). Moving toward wider implementation, a retrospective cohort study found that group prenatal care implemented through Centering Pregnancy affected the rate of preterm birth, particularly among Black women (58). With relevance to policy, using a quasi-experimental study design, participation in a Medicaid-enhanced prenatal health program reduced the risk of adverse birth outcomes (44). However, 2 prenatal home visitation RCTs showed no significant effects on preterm birth (59) and adverse birth outcomes (60). In a randomized controlled trial, among pregnant adolescents enrolled in a nurse home visitation program pre- and postnatally, infants in the intervention group had higher cognitive development scores for gross motor and cognitive domains (Bayley Scales of Infant and Toddler Development III) than infants who received health care as usual (43). Interestingly, in this small study, intervention effects were mediated by DNA methylation (43), suggesting that epigenetic changes could be a mechanism through which prenatal structural interventions could improve fetal development (61), possibly also with implications for neurodevelopment.

Poverty-reduction interventions such as transferring cash to families in need have also shown promising results for improved postnatal development. Prenatal cash transfer programs, like the Mexican Oportunidades program and the Uruguayan Plan de Atención Nacional a la Emergencia Social program, resulted in improved birth weight outcomes through enhanced maternal nutrition and prenatal care quality (46,47). Further, given recent findings associating neighborhood violence with offspring brain functional connectivity, partly mediated by prenatal maternal psychosocial

stress, studies examining community-led safety interventions are needed (62).

Evaluating the impact of structural interventions during pregnancy on offspring neurodevelopment is an overdue next step needed to help curtail cycles of intergenerational transmission of adversities. However, the effects of these interventions on maternal mental health were not examined in the aforementioned studies, missing a critical opportunity to understand mechanisms and maximize possible prenatal programming effects.

Considerations for Studies of Prenatal Maternal Interventions Measuring Offspring Brain and Neurodevelopment: Limitations and Recommendations for Future Research

The intervention approaches reviewed in this article are strategies that may promote offspring healthy brain development and prevent the intergenerational effects of risk for psychopathology, yet there are limitations in the Developmental Origins of Health and Disease evidence base. In many instances, the studies needed have not yet been conducted, and as a result, overinterpretation of studies' results is common. RCTs of interventions during pregnancy that include maternal mental health–relevant outcomes during pregnancy and offspring outcomes are needed to verify if fetal exposures to maternal stress and distress-based biological processes can be modifiable and—if and when modified—could influence fetal development (63,64).

Future RCTs should consider several key challenges. First are the difficulties in measuring child neurodevelopmental outcomes. Whereas researchers now have the option of assessing neurodevelopment in infancy using evolving neuroimaging techniques (65), these are high cost and labor intensive. Alternatively, one needs to rely on maternal self-report assessments of child behavior and emotional problems, introducing potential biases (66,67). Intermediate markers of biological processes, such as DNA methylation (68), telomere length (69), or indicators of inflammatory processes (70), could allow RCTs to test whether experimentally induced improvements in maternal mental health may affect biological processes of infant development; however, more work is still required to link these biological process indicators to infant neurodevelopment. Adding to the challenge, RCTs are expensive and typically powered as intention-to-treat analyses, making secondary analyses to detect effects on offspring underpowered. In addition, existing intervention studies often target one perinatal exposure of interest (e.g., nutrition, exercise, or depression), while effects of multiple exposures are the norm and may have a synergistic effect on infant brain behavior development. In terms of effect modifiers, sex differences deserve particular attention, especially as they may be influenced by maternal biology (71–73). Timing of implementation is also critical; it may be that for some interventions (e.g., physical activity), the prenatal period may present too many competing challenges (e.g., fatigue) that make this sort of lifestyle modification harder to adhere to. The preconception period may offer unique opportunities that remain largely untested.

Adequately assessing intergenerational effects will thus require rethinking the RCTs currently being conducted in several ways. First, intergenerational RCTs will need to be framed explicitly as such, defining offspring neurodevelopmental outcomes as primary targets and the specific maternal intervention target improvement as the main mediator of interest. This means focusing on offspring, rather than mothers, to define sample sizes to ensure adequate statistical power. Second, studies will need to use rigorous methods to control for competing explanations and mediators, particularly by measuring postnatal exposures and examining downstream intervention effects. Third, studies will also need longer-term offspring follow-ups, as, with few exceptions to date, studies have mostly detected early signs (in infancy and toddlerhood) of risk for future psychopathology. Fourth, structural interventions, if shown effective, will require policy change, necessitating collaboration with policy sectors and advocates. Finally, interventions using medication and those aimed at decreasing or preventing tobacco, alcohol, and other substance use in pregnancy were intentionally excluded from this review in recognition of space limitations and the sheer size of this body of literature. Nonetheless, this is an area of intervention critical to maternal and offspring well-being.

A key limitation in perinatal mental health intervention research affecting offspring neurodevelopment is the lack of studies that include sufficient numbers of underserved and marginalized individuals and those who can access the types of interventions offered, which limits the generalizability of the knowledge base as well as its application to those likely most in need. Our umbrella review of SRMA of studies that could yield strong causal conclusions (RCTs), for example, mostly included studies in high-income countries. Unfortunately, within the United States, the last 3 decades have not seen increases in participation of racially and ethnically minoritized individuals parallel to the U.S. population distributions, even after the passing of the National Institutes of Health Revitalization Act in 1993 (74,75). In 2020, Latine and Black individuals represented only 16% of clinical trial participants, when these populations constitute a third of the U.S. population. Relying on samples that are neither diverse nor representative poses both a scientific and an ethical challenge. The effects of structural racism and discrimination as well as of other inequities can result in inequities in health conditions, including mental health conditions, access to care for these conditions, and likely deficient understanding of etiological and treatment processes.

In sum, the perinatal period is a critical moment for pregnant populations and offspring neurodevelopment. It is full of challenges and potential risks for psychopathology but is also characterized by increased points of contact with the health care system. Intergenerational studies suggest that this period may be an unmatched opportunity not only for improving maternal health and well-being but also for the prevention of offspring psychopathology. Although the prenatal programming literature has grown at an impressive rate in the last decades, assessment of offspring effects following interventions during pregnancy lag significantly behind. To date, the different interventions reviewed here show some promise in improving maternal health and deterring intergenerational transmission but are limited in the number that have rigorously studied offspring outcomes by the lack of existing RCTs, and therefore preclude firm conclusions on how effective any of the intervention types considered are in protecting infant brain-

behavior development. These challenges however are not unsurmountable; the next generation of studies should be able to decipher the impact that prenatal maternal interventions can have on offspring neurodevelopment.

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