Research Review: Developmental origins of depression – a systematic review and meta-analysis

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Background: Many observational studies have found a direct association between adverse in utero, perinatal and postnatal exposures and offspring’s depression. These findings are consistent with the ‘developmental origins of disease hypothesis’. But no review has comprehensively summarized the roles of these exposures. This review aims to systematically scrutinize the strength of associations between individual prenatal, perinatal, and postnatal exposures and subsequent depression in offspring. Methods: We conducted a systematic review and meta-analysis to synthesize the literature from the EMBASE, HealthStar, PsychInfo, and Medline databases since their inception to September 1, 2019. English language articles on population-based prospective cohort studies examining the associations between in utero, perinatal, and postnatal exposures and offspring’s depression were searched. Random-effects models were used to calculate pooled estimates, and heterogeneity and sensitivity tests were conducted to explore potential confounders in the relationships of depression and early-life factors. Qualitative analysis was also conducted. Results: Sixty-four prospective cohort studies with 28 exposures studied in the relationships to offspring’s depression met inclusion criteria. The meta-analysis found 12 prenatal, perinatal, and postnatal characteristics had no effects on conclusions. Qualitative analyses generally supported the findings of meta-analysis and reported on additional risk factors. Conclusions: This review provides a robust and comprehensive overview of the lasting psychopathological effects of in utero, perinatal, and postnatal exposures. The findings highlight the need for clinical and public health interventions focusing on the identified risk factors. Large prospective cohort studies are warranted to investigate the combined effects of multiple co-existing early-life exposures. Keywords: Depression; in utero exposures; perinatal exposures; risk factors; children.

Introduction

Major depression is a public health problem internationally, especially in high- and upper-middle-income countries (Rehm & Shield, 2019). It is estimated that major depression was one of the five leading causes (out of 328) of years lived with disability (YLDs) in 195 countries and territories from 1990 to 2016, contributing 34.1 million years to the total YLDs (Vos et al., 2015). Accumulating evidence shows adverse conditions in pregnancy and early life are associated with later negative neuropsychiatric outcomes (Hazel, Hammen, Brennan, & Najman, 2008; Newman et al., 2016; Strüber, Strüber, & Roth, 2014). Adverse in utero and perinatal exposures were associated with mental health status in adolescence and adulthood. The association between adverse in utero and perinatal exposures and mental health outcomes in later adulthood could involve alternations in cellular aging (Entringer et al., 2011). The alternations of cellular aging could then trigger epigenetic modifications and increase the susceptibility of mental disorders among affected individuals (Vaiserman & Koliada, 2017). Although there is evidence that adverse in utero and perinatal exposures are associated with subsequent health outcomes in adolescence and adulthood, the underlying mechanisms of the ‘biological embedding’ of early-life experiences are not sufficiently understood. Empirical studies on fetal programming effects have shown that maternal stress or undernutrition leads to fetal growth retardation, which compromises in fetal development and growth linking with early onset of adult diseases (Calkins & Devaskar, 2011). The developmental origins of health and disease (DOHaD) model highlights the roles for in utero, perinatal, and postnatal factors in the development of major depression during the life course (O’Donnell & Meaney, 2017). However, as mental disorders are complex diseases involved multiple risk factors, the causal conclusions between the in utero and perinatal exposures and adolescent and adult mental health status warrant further investigation.

The following mechanisms have been proposed to understand the associations between prenatal and perinatal factors and subsequent psychopathology, including (a) intergenerational transmission of maternal stress (Hentges, Graham, Plamondon, Tough, & Madigan, 2019), (b) low birth weight has

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been associated with impaired executive function, educational achievements, and an elevated risk of major depression (Aizer & Currie, 2014), (c) antenatal maternal emotional wellbeing has been closely linked with offspring’s neurodevelopmental outcomes (Glover, 2014; Pearson et al., 2013), (d) glucocorticoids have been shown to mediate the association between maternal adversities and offspring development (Desplats, 2015; Meaney, Szyf, & Seckl, 2007), and (e) the integration of genetic and prenatal environmental factors on DNA methylation is seen to have enduring influences on normal development and health (Czamara et al., 2019).

While an increasing number of observational studies has found that several prenatal, perinatal, and postnatal factors increased the risk of depression across the life span, most of these studies were cross-sectional leaving them open to the criticism that cross-sectional designs increase the likelihood of contributing spurious associations between these factors and depression (Betts, Williams, Najman, & Alati, 2015; Fryer, McGee, Matt, Riley, & Mattson, 2007; Owens & Hinshaw, 2013; Quarini et al., 2016; Richardson et al., 2016; Whelan, Leibenluft, Stringaris, & Barker, 2015). There is a lack of systematic evidence that comprehensively summarizes the factors during early life that contribute to the development of depression. A critical review of these in utero, perinatal, and postnatal conditions not only stimulates possible etiological explanations of the reported associations in depression but also suggests directions for care and prevention services to provide adequate and appropriate support to those with identified risk factors. We are not aware of any systematic review of in utero, perinatal, and postnatal factors on depression that comprehensively synthesizes those attributes associated with the risk of depression. This present review aims to objectively evaluate the role of each early-life exposure (occurring after conception, before or after birth (up to 1 year old), or characteristics of the perinatal environment) in major depression or depressive symptoms across the life span. The exposures were grouped into biological, psychological, and sociological factors based on the biopsychosocial model proposed by Engel (1977) which provides a fundamental framework to systematically consider the roles of biological, psychological, and sociological factors in the process of disease and health. This model endorsed a holistic approach, linking normality to abnormality through biological and psychosocial mechanisms (Frazier, 2020). Findings of this review could add new knowledge to the DOHaD hypothesis by clearly showing the factors that are robustly associated with depression and draw attentions to these identified factors noting their importance and the necessity for high quality maternal and child care to address them.

## Methods

### Search strategy

This systematic review and meta-analysis are guided by the Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklists (Table S1) (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009; Stroup et al., 2000). The protocol of this study was registered in PROSPERO, number CRD42019147074. We searched for prospective longitudinal studies on in utero, perinatal/postnatal exposures. These exposures included birth weight, baby’s length at birth, birth order, gestational age (GA), small gestational age (SGA), socioeconomic status at birth, maternal education, teen parents, parental age greater than 35 years of age, single mother, maternal stress, maternal anxiety, maternal pre- and postnatal depression, exposure to maternal drinking, maternal smoking and paternal smoking, and exposure to bisphenol A, fetal antiepileptic drug, selective serotonin reuptake inhibitors, antibiotics, organic pollutants, elemental carbon attributable to traffic (ECAT), marijuana, cocaine, famine, maternal infection, and maternal chronic disorders. We first conducted a computerized search for bibliographic databases, including EMBASE, HealthStar, PsychInfo, and Medline from their inception until September 1, 2019 for published articles on the above-mentioned maternal and child conditions and major depression. The detailed search strategies for each database are fully described in Appendix S1. We then applied a snowball technique to search the reference lists of all relevant studies for further potential studies. In addition, we manually searched other resources to maximize the relevant studies. The reference lists of selected articles, review articles on relevant topic, and the gray literature were all screened. Only articles published in English were included.

### Eligibility criteria

Articles that met the following criteria were included in this systematic review: (a) population: had a clear diagnosis for major depression or depressive symptoms, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) and its updates, International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) or other generally accepted criteria; (b) phenomenon of interest: provided the information on in utero, perinatal, or early-life exposures; (c) comparison: had a comparison group (s) without the exposure(s); (d) outcome: provided statistical indicators to examine the impact of in utero and perinatal factors on major depression across the life span; and (e) study design: were longitudinal cohort studies, including population-based cohort studies and registry-based studies.

### Selection of the studies

Two researchers (YS and XM) independently screened and selected the retrieved articles by titles and abstracts, followed by full texts. An article was discarded if both reviewers agreed that the article did not meet the inclusion criteria. Inconsistencies in interpretation were resolved through group discussions among the authors. Endnote and RefWorks were used as bibliographic software.

### Data extraction, synthesis, and quality assessment

Data on first author(s), year of publication, study site, sample size, age of offspring at enrollment, length of follow-up, type of depression, prenatal, perinatal, and postnatal factors, measures of major depression or depressive symptoms, other covariates, and major results were extracted independently. If there were multiple reports from a single cohort, only the
record with more complete information was extracted. If there were any discrepancies in reports, we contacted the study authors for clarification. Any disagreements were solved by group discussions. For those articles which did not have the data to calculate the pooled estimates, we provided a narrative description instead and kept the results for qualitative analysis. And if several studies were from the same cohort study with the same exposures, the one with the longest follow-up time was chosen for analysis.

The reviewers endeavored to contact the original authors of the studies with missing information to gather complete information. We offered open-ended questions to prevent the skewness of responses. The methodological quality of the included studies was assessed by the Newcastle–Ottawa Scale (NOS) for assessing the quality of cohort studies (Wells, 2001). The NOS rating is composed of eight items covering three domains: selection of study groups, comparability of case and comparison groups, and ascertainment of outcome or exposure. The total score of the NOS ranges between 0 and 9. The scores of good quality studies ranged from 7 to 9, studies scoring 6 were judged fair, and those scoring <5 were considered poor.

This review included both quantitative and qualitative analyses for the selected articles. For the quantitative analysis only, original studies with the necessary data to calculate an odds ratio were included, whereas the qualitative synthesis included the rest of the studies for which odd ratios could not be calculated or could not be synthesized by meta-analysis due to high heterogeneity. These later studies had diverse categorizations of variables, or statistical indicators that could not be translated into odds ratios. Or they were included in the qualitative analysis because of the limited number of available studies on a given risk factor. A total of 64 articles were included in this review. Of the included studies, 29 reported only quantitative results, 31 reported only qualitatively analyzed results, and four reported both quantitative and qualitative results. As a result, 33 studies were used in the meta-analysis and 35 studies were qualitatively synthesized. We report results of both the quantitative and qualitative syntheses based on the studied exposure.

**Meta-analysis**

DerSimonian and Laird $I^2$ statistics were used to test heterogeneity across studies. We used both funnel plots and Egger/Begg tests to examine publication bias. Compared with funnel plots, the Egger test provides a more objective way to estimate the reliability of the results. We then applied the trim and fill method to explore potential publication bias. Based on the results of heterogeneity tests, random-effects model was used to calculate pooled estimates, which is more conservative compared to fixed-effects model. Meta-regression analysis was conducted to identify possible explanations for the heterogeneity. Sensitivity analysis was also performed to explore the effects of the potential confounders. We did subgroup analysis for different prenatal and perinatal/postnatal factors. Analyses were conducted using RevMan version 5.3 and Stata version 15.0.

**Results**

We started with a total of 9,418 titles from the four bibliographic databases. A total of 4,293 duplicates were then removed. A total of 1,392 articles were identified as eligible studies for full-text review with 1,328 being subsequently excluded for detailed reasons. After applying the inclusion criteria, 64 studies remained for this systematic review and meta-analysis. A flowchart of the study selection process is presented in Figure 1.

Table S2 presents a summary of the characteristics of 64 studies reviewed (Alati et al., 2007; Barker, Copeland, Maughan, Jaffee, & Uher, 2012; Betts, Salom, Williams, Najman, & Alati, 2015; Biederman, Martelon, Woodworth, Spencer, & Faraone, 2017; Buizer-Voskamp et al., 2011; Butler, 2014; Chiu et al., 2019; Cohen et al., 2013; Colman, Attaullahjan, Naicker, & Van Lieshout, 2012; Elmasry, Goodwin, Terry, & Tehranifar, 2014; Fan & Eaton, 2001; Fergusson, Woodward, & Horwood, 1998; Gale & Martyn, 2004; Geoffroy, Gunnell, Clark, & Power, 2018; Gray, Day, Leech, & Richardson, 2005; Harley et al., 2013; Herva et al., 2008; Johnson, O’Reilly, Ni, Wolke, & Marlow, 2019; Joinon, Kounali, & Lewis, 2017; Kiff et al., 2012; Kingsbury et al., 2016; Leung, Leung, & Schooling, 2015; Levine, 2014; Levy-Shiff et al., 1994; Li et al., 2018; Liu et al., 2011; Loret de Mola et al., 2015; Malm et al., 2016; Meier et al., 2017; Menezes et al., 2013; Murphy et al., 2017; Nomura, Brooks-Gunn, Davye, Ham, & Fifer, 2007; Nomura, Wickramaratne, et al., 2007; O’Connor & Kasari, 2000; Pawłowski, Hay, Sharp, Waters, & O’Keane, 2009; Pearson et al., 2013; Pereira et al., 2012; Perera et al., 2016; Perquier, Lasfargues, Mesrine, Clavel-Chapelon, & Fagherazzi, 2014; Phillips, Hammen, Brennan, Najman, & Bor, 2005; Pitzer, Jennen-Steinmetz, Esser, Schmid, & Laucht, 2011; Plant, Pariante, Sharp, & Pawly, 2015; Power et al., 2007; Ramchandani et al., 2008; Raposa, Hammen, Brennan, & Najman, 2014; Richardson, Goldschmidt, Larkby, & Day, 2013; Saigal, Pinelli, Hoult, Kim, & Boyle, 2003; Slykerman et al., 2015, 2017; Sonon, Richardson, Cornelius, Kim, & Day, 2016; Strom et al., 2014; Taka-Eilola Nee Riekkki, Veijola, Murray, Koskela, & Maki, 2019; Taylor et al., 2017; Tearn et al., 2016; Tracy, Salo, Slopen, Udo, & Appleton, 2019; Tuovinen et al., 2014; Van Lieshout & Boylan, 2010; Wang, Leung, Lam, & Schooling, 2015; Westrupp, Northam, Doyle, Callanan, & Anderson, 2011; Yamasaki et al., 2019; Yolton et al., 2019; Zohsel et al., 2019). Of the 64 studies, 18 studies were conducted in the United States, 13 in United Kingdom, 6 in Australia, 3 in Canada, 4 in Finland, 1 in France, 4 in China, 2 in Denmark, 2 in Germany, 4 in Brazil, 1 in Japan, 3 in New Zealand, 1 in Netherlands, 1 in Norway, and 1 in Israeli. The NOS score of study quality for the included studies ranged from 4 to 9 with the median score of 6.9. This review includes mostly good quality studies. Thirty-eight of the studies were judged to be good quality studies, and 25 were rated as being of fair quality with one study rated as poor. Details of study quality can be found in Table S3. Of the studies reporting quantitative results, 17 were judged as being of good quality studies, 16 were judged as being of fair quality. Of the studies reporting qualitatively synthesized
results, 21 were judged to be good quality, nine were judged fair, and one was poor quality.

Table 1 provides a concise summary of the meta-analysis’s findings. Of the 28 early-life exposures studied, a total of 12 prenatal and perinatal/postnatal factors were significantly associated with offspring’s depression, namely low birth weight, premature birth, SGA, maternal education, socioeconomic position, having younger parents (< 20 years old), having older parents (≥ 35 years), maternal smoking, paternal smoking, maternal stress, maternal anxiety, and prenatal depression. Forest plots of the studied individual and pooled odds ratios are presented in Figure 2. Heterogeneity tests for most of the studied variables were not significant (p > 0.05) with exceptions being socioeconomic status (SES), maternal smoking, maternal prenatal depression, low birth weight, and GA. Since high heterogeneity was found for the pooled estimates for some risk factors, we used meta-regression analyses to explore if age onset of depression (≤ 17 and > 18 year of old) could explain the heterogeneity across the selected studies. The univariate meta-regression showed that age of onset had a significant impact on the heterogeneity across studies. Table S4 displays the results of the meta-regression models.

Because some exposures only had one publication in the selected studies, we then applied qualitative approach to synthesize these exposures instead. Additionally, studies with either diverse categorization or statistical indicators that could not be converted into odds ratios were also summarized as qualitatively analyzed studies. Noteworthy, although some studies presented the findings with odds ratios, their categorizations of exposures could not be harmonized thus these studies were described qualitatively. Detailed results from these qualitatively analyzed studies are reported in Table S5. These qualitatively analyzed studies are also noted by the # symbol in Table S2. Although there are some overlapped risk factors between qualitatively and quantitatively analyzed studies, there are some risk factors that are unique to the qualitatively analyzed studies. All qualitatively analyzed results are summarized in Table 2.

Biological factors

Low birth weight. Ten studies were included in the meta-analysis (Alati et al., 2007; Gale & Martyn, 2004; Geoffroy et al., 2018; Herva et al., 2008; Levine, 2014; Nomura, Brooks-Gunn, et al., 2007; Nomura, Wickramaratne, et al., 2007; Pereira et al., 2012). The findings indicated that low birth weight (< 2,500 g) was associated with an elevated risk of depression, with a pooled OR of 1.44 (95% CI, 1.17–
Psychological factors

1.76, k = 10, N = 27,574). There was a high degree of heterogeneity between studies ($I^2 = 62\%$, $p < .01$). Visual assessment of a funnel plot, and Egger as well as Begg test provided no evidence of obvious publication bias.

However, the findings in the qualitative analysis were mixed (k = 7). Three of seven studies reported an association between low birth weight and depression (Levy-Shiff et al., 1994; Loret de Mola et al., 2015; Van Lieshout & Boylan, 2010). In contrast, two studies found no association between birth weight and major depression (OR = 0.91; 95%CI, 0.82–1.01; OR = 1.15; 95%CI, 0.96–1.36) (Betts, Salom, et al., 2015; Perquier et al., 2014). Two additional studies, one on very low birth weight (<1,500 g) and the other on extremely low birth weight (<1,000 g) did not find any association between low birth weight and depression (Saigal et al., 2003; Westrupp et al., 2011) (Details could be found in Table S5).

Gestational age. In the meta-analysis of seven studies (Chiu et al., 2019; Herva et al., 2008; Levine, 2014; Loret de Mola et al., 2015; Nomura, Brooks-Gunn, et al., 2007; Pereira et al., 2012), premature children (<37 weeks) were found at an elevated risk of depression (OR = 1.38; 95%CI, 1.00–1.90, k = 7, N = 128,001) and there was a high degree of heterogeneity between studies ($I^2 = 62\%$, $p = .02$). No obvious publication bias was observed from visual assessment of a funnel plot or Egger/Begg test.

In contrast, the findings of qualitatively analyzed studies (k = 4) on the relationship between gestational age and depression were generally negative. One study reported that gestational age was linked with a higher risk of offspring’s depression ($r = .82$, $p < .001$) (Levy-Shiff et al., 1994), whereas three studies found no statistical evidence of such association including one study on extremely preterm children (<26 weeks) (Cohen et al., 2013; Johnson et al., 2019; Wang et al., 2015).

Small gestational age at birth. The meta-analysis of three studies suggested that being small for gestational age at birth was more likely to lead to major depression (OR = 1.46; 95%CI, 1.11–1.94, k = 3, N = 6,165) (Colman et al., 2012; Fan & Eaton, 2001; Slykerman et al., 2015). There was no evidence of heterogeneity between studies ($I^2 = 0\%$, $p = .72$). Visual inspection of a funnel plot, and Egger as well as Begg test provided no evidence of obvious publication bias.

In the qualitative analysis, one study found small gestational age was associated with an increased risk of depression onset only in adolescence but not in childhood (adolescence = 2.70, $p < .01$; childhood = 0.15, $p < .88$) (Van Lieshout & Boylan, 2010). It supported our significant findings of a pooled OR of 1.46.

Birth order. The meta-analysis of five studies found that there was no statistical association between birth order and depression (OR = 1.08; 95%CI, 0.91–1.29, k = 5, N = 21,246), when comparing individuals who were second born or later to those who were first born individuals (Betts, Salom, et al., 2015; Geoffroy et al., 2018; Herva et al., 2008; Pereira et al., 2012). There was no evidence of heterogeneity between studies ($I^2 = 30\%$, $p = .22$). The visual inspection of the funnel plot and Begg test did not indicate any evidence of publication bias. However, the Egger test found significant publication bias ($p = .031$).

Baby’s length at birth. One qualitative study reported null association between baby’s birth

### Table 1 A summary table of the meta-analysis findings

| Factors                                | Number of studies | Odds Ratio | 95%CI     | Find significant association |
|----------------------------------------|-------------------|------------|-----------|-----------------------------|
| **Biological factors**                 |                   |            |           |                             |
| Low birth weight (<2,500 g)            | 10                | 1.44       | 1.17, 1.76| Yes                         |
| Gestational age (Premature children < 37 weeks) | 7                | 1.38       | 1.00, 1.90| Yes                         |
| Small gestational age                   | 3                 | 1.46       | 1.11, 1.94| Yes                         |
| Birth order                            | 5                 | 1.08       | 0.91, 1.29| No                          |
| Teen parents (<20 years old)           | 9                 | 1.46       | 1.22, 1.74| Yes                         |
| Parents’ age >35 years                 | 6                 | 1.13       | 1.07, 1.20| Yes                         |
| **Psychological factors**              |                   |            |           |                             |
| Maternal stress                        | 4                 | 1.12       | 1.04, 1.22| Yes                         |
| Maternal anxiety                       | 2                 | 1.09       | 1.02, 1.17| Yes                         |
| Maternal prenatal depression           | 8                 | 1.36       | 1.07, 1.72| Yes                         |
| Maternal postnatal depression          | 3                 | 1.52       | 0.92, 2.50| No                          |
| **Sociological factors**               |                   |            |           |                             |
| Maternal education (<9 years of study) | 9                 | 1.37       | 1.19, 1.57| Yes                         |
| Socioeconomic status (Low)             | 6                 | 1.29       | 1.10, 1.52| Yes                         |
| Single mother                          | 2                 | 1.20       | 0.64, 2.25| No                          |
| Maternal smoking                       | 13                | 1.45       | 1.28, 1.63| Yes                         |
| Paternal smoking                       | 4                 | 1.28       | 1.11, 1.48| Yes                         |
| Maternal drinking                      | 2                 | 1.09       | 0.96, 1.24| No                          |
length and depression (Perquier et al., 2014). There were no comparable meta-analysis findings.

**Age of parents.** There were nine studies exploring the association between having teen parents (<20 years old) and depression in offspring in the meta-analysis (Buizer-Voskamp et al., 2011; Geoffroy et al., 2018; Herva et al., 2008; Levine, 2014; Pereira et al., 2012; Slykerman et al., 2015). The findings showed that having teen parents elevated the risk of offspring’s depression (OR = 1.46; 95% CI, 1.22–1.74, k = 9, N = 93,850) and there was no
Likewise, in the meta-analysis of six studies (Buizer-Voskamp et al., 2011; Pereira et al., 2012; Slykerman et al., 2015), we found that offspring who had parents 35 years of age and older also reported a higher risk of depression (OR = 1.13; 95% CI, 1.07–1.20, k = 6, N = 73,208). There was no evidence of heterogeneity between studies ($I^2 = 0\%$, $p = .60$). No obvious publication bias was observed from the visual assessment of a funnel plot nor Egger/Begg test for both of the exposures.

A total of four qualitatively analyzed studies explored the relationship between having teen parents and the risk of depression in offspring, with 3 of 4 studies reported a positive association (Kiff et al., 2008).

| Factors                          | Number of studies | Results | Major findings                                                                 |
|---------------------------------|-------------------|---------|--------------------------------------------------------------------------------|
| Biological factors              |                   |         |                                                                                |
| Low birth weight                | 7                 | Negative (4) | Three studies reported an association between low birth weight and depression in offspring, while four studies reported null association. |
| Gestational age                 | 4                 | Negative (3) | One study reported an association between preterm birth and depression in offspring, while three studies reported null association. |
| Small gestational age           | 1                 | Positive  | One study reported an association between small gestational age and depression in offspring in adolescence. |
| Baby’s length at Birth          | 1                 | Negative  | One study reported null association between birth length and depression in offspring. |
| Teen parents                    | 4                 | Positive (3) | Three studies reported an association between having teen parents and depression in offspring, while one study reported null association. |
| Parents’ age >35 years          | 1                 | Positive  | One study reported an association between having elderly parents and depression in male offspring. |
| Maternal infections             | 2                 | Mixed    | One study reported an association between maternal infections and depression in offspring, while one study reported null association. |
| Chronic diseases                | 2                 | Positive  | Two studies reported that maternal hypertensive disorder and diabetes were associated with an elevated risk of depression in offspring, respectively. |
| Bisphenol A                     | 2                 | Positive  | Two studies reported an association between Bisphenol A and depression in offspring. |
| Fetal antiepileptic drug        | 1                 | Negative  | One study reported null association between fetal antiepileptic drug and depression. |
| SSRIs                           | 1                 | Positive  | One study reported an association between SSRIs and depression in offspring. |
| Antibiotics                     | 1                 | Positive  | One study reported an association between antibiotics use and depression in offspring. |
| Organic pollutants              | 1                 | Negative  | One study reported null association between fetal exposure to persistent organic pollutants and depression. |
| ECAT                            | 1                 | Positive  | One study reported an association between prenatal ECAT exposure and depression in offspring. |
| Marijuana exposure              | 2                 | Positive  | Two studies reported an association between maternal marijuana exposure and depression in offspring. |
| Cocaine exposure                | 1                 | Negative  | One study reported null association between cocaine exposure and depression. |
| Psychological factors           |                   |         |                                                                                |
| Maternal stress                 | 2                 | Mixed    | One study reported an association between maternal stress and depression in offspring, while one study reported null association. |
| Maternal prenatal depression    | 1                 | Negative  | One study reported an association between maternal prenatal depression and depression in offspring, while one study reported null association. |
| Paternal postnatal depression   | 1                 | Negative  | One study reported null association between paternal postnatal depression and depression in offspring. |
| Sociological factors            |                   |         |                                                                                |
| Socioeconomic status            | 2                 | Mixed    | One study reported an association between low socioeconomic status and depression in offspring, while one study reported null association. |
| Maternal smoking                | 4                 | Negative (3) | One study reported an association between maternal smoking and depression in offspring, while three studies reported null association. |
| Maternal drinking               | 3                 | Positive (2) | Two studies reported an association between maternal drinking and depression in offspring, while one study reported null association. |
| Famine                          | 1                 | Positive  | One study reported null association between famine in utero and depression in offspring. |

ECAT, Elemental carbon attributable to traffic; SSRIs, Selective serotonin reuptake inhibitors.

*Risk factors found to be significantly associated with offspring’s depression in the meta-analysis.

evidence of heterogeneity between studies ($I^2 = 32\%, p = .16$).
2012; Slykerman et al., 2015; Tracy et al., 2019). One study reported non-significant findings (Tearne et al., 2016).

Additionally, the only qualitatively analyzed study reported that parental age greater than 35 years increased the risk of depression for girls but not for boys (Tearne et al., 2016).

Physical health problems. There was no meta-analysis on the exposure of physical health problems due to the limited number of eligible studies. Qualitatively analyzed findings ($k = 4$) on maternal infections were inconsistent, including one study reporting an elevated risk of depression among offspring (Murphy et al., 2017), and non-significant findings in another study (Betts, Salom, et al., 2015). Two studies reported that maternal hypertensive disorder and diabetes were associated with an elevated risk of depression among offspring, respectively (Tuovinen et al., 2014; Yamasaki et al., 2019).

Chemical, and drug exposures. There is only qualitative synthesis available for the chemical and drug exposures. We did not perform a meta-analysis for these factors because of limitations in available studies and high heterogeneity in the measurement of these exposures. A total of eight chemical or drug exposures have been studied to explore their effects on offspring’s depression, including bisphenol A (BPA), fetal antiepileptic drug, selective serotonin reuptake inhibitors, antibiotics, organic pollutants, elemental carbon attributable to traffic (ECAT), marijuana exposure, and cocaine exposure. Prenatal BPA exposure was consistently found to be associated with an elevated risk of depressive symptoms and depression in boys (Harley et al., 2013; Perera et al., 2016). In terms of drugs, prenatal SSRI exposure (Malm et al., 2016), antibiotics use (Slykerman et al., 2017), prenatal or early-life exposure to elemental carbon attributable to traffic (ECAT) (Yolton et al., 2019), and maternal marijuana exposure (Gray et al., 2005; Sonon et al., 2016) were associated with an elevated risk of depression. There were no statistical associations between offspring’s depression and exposure to fetal antiepileptic drug (Cohen et al., 2013), persistent organic pollutants (Strom et al., 2014), and maternal cocaine use (Richardson et al., 2013).

Psychological factors

Maternal stress. The meta-analysis of four studies found that: (1) maternal stress was associated with offspring’s depression ($OR = 1.12$; 95% CI, 1.04–1.22, $k = 4$, $N = 2,582$) (Phillips et al., 2005; Pitzer et al., 2011; Slykerman et al., 2015). There was no evidence of heterogeneity between studies ($I^2 = 0%$, $p = .91$); and (2) prenatal maternal stress (two studies) was associated with the increased risk of depression with the pooled odds ratio of 1.09 (95%CI, 1.04–1.14, $k = 2$, $N = 1,157$), and there was no evidence of heterogeneity between studies ($I^2 = 0%$, $p = .91$); and (3) maternal postnatal stress (two studies) was similarly reported to elevate the risk of depression among offspring ($OR = 1.27$; 95%CI, 1.07–1.51, $k = 2$, $N = 1,425$). No evidence of heterogeneity between studies was found ($I^2 = 7%$, $p = .30$). Visual inspection of funnel plots, and Egger as well as Begg tests provided no evidence of obvious publication bias.

The qualitative analyzed findings ($k = 2$) on the relationship between maternal stress and offspring’s depression risk are mixed, with one study finding a positive relationship whereas another did not (Gray et al., 2005; Murphy et al., 2017).

Maternal anxiety. The meta-analysis of two studies found that maternal anxiety increased the risk of depression ($OR = 1.09$; 95% CI, 1.02–1.17, $k = 2$, $N = 13,127$) and there was no evidence of heterogeneity between studies ($I^2 = 0%$, $p = .84$) (Betts, Salom, et al., 2015; Herva et al., 2008; Kingsbury et al., 2016; Pawlby et al., 2009; Pearson et al., 2013; Plant et al., 2015; Taka-Eilola Nee Riekkki et al., 2019; Zohsel et al., 2017). There was a statistically significant heterogeneity ($I^2 = 76%$, $p < .01$). The visual inspection of the funnel plot and Begg test did not indicate any evidence of publication bias. However, the result of Egger test found significant publication bias ($p = .032$).

In the two qualitatively analyzed studies ($k = 2$), maternal prenatal depression was significantly associated with depressive symptoms in one study (Gray et al., 2005), but not in another (Raposa et al., 2014).

Parental postnatal depression. Our meta-analysis of three studies found no statistically significant association between maternal postnatal depression and offspring’s depression ($OR = 1.52$, 95%CI, 0.92–2.50, $k = 3$, $N = 10,379$) (Barker et al., 2012; Pearson et al., 2013; Plant et al., 2015). There was no evidence of heterogeneity between studies ($I^2 = 55%$, $p = .11$). Visual inspection of a funnel plot, and Egger as well as Begg test provided no evidence of obvious publication bias.

In the qualitative study, one study reported a null association between paternal postnatal depression and depression in their offspring (Ramchandani et al., 2008), which is consistent with other findings in this systematic review.
Sociological factors

Education. Our meta-analysis of nine studies found that low maternal education (<9 years of study) was associated with the elevated risk of depression \((OR = 1.37; 95\%\, CI, 1.19–1.57, k = 9, N = 41,768)\) (Betts, Salom, et al., 2015; Herva et al., 2008; Joinson et al., 2017; Kingsbury et al., 2016; Pereira et al., 2012; Tracy et al., 2019). There was no evidence of heterogeneity between studies \(I^2 = 40\%,\, p = .10\). No evidence of obvious publication bias was observed based on the visual assessment of a funnel plot and the Egger/Begg test.

SES. Six studies were included in the meta-analysis investigating the relationship between SES and depression in offspring (Herva et al., 2008; Joinson et al., 2017; Kingsbury et al., 2016; Slykerman et al., 2015). The results suggested that low SES was associated with a higher risk of depression \((OR = 1.29; 95\%\, CI, 1.10–1.52, k = 6, N = 28,710)\). There was a statistically significant heterogeneity \(I^2 = 60\%,\, p = .03\). No obvious publication bias was found from visual inspection of a funnel plot, and Egger as well as Begg test.

Two other qualitatively analyzed studies \(k = 2\) had mixed findings, with one study reporting a significant relationship between low SES and an increased risk of depression and the other found no association (Butler, 2014; Power et al., 2007).

Having a single mother. The meta-analysis including two studies found that having a single mother did not increase a child’s risk of depression \((OR = 1.20; 95\%\, CI, 0.64–2.25, k = 2, N = 1,444)\) (Pereira et al., 2012). There was no evidence of heterogeneity between studies \(I^2 = 41\%,\, p = .19\). No obvious publication bias was observed from visual inspection of a funnel plot, and Egger as well as Begg test.

Parental smoking. There were 13 studies exploring the association between maternal smoking and depression risk in offspring (Betts, Salom, et al., 2015; Biederman et al., 2017; Elmasry et al., 2014; Herva et al., 2008; Kingsbury et al., 2016; Levine, 2014; Meier et al., 2017; Menezes et al., 2013; Pereira et al., 2012; Taylor et al., 2017). Maternal smoking was associated with the increased risk of depression in the meta-analysis \((OR = 1.45; 95\%\, CI: 1.28–1.63, k = 13, N = 823,532)\). There was a statistically significant heterogeneity \(I^2 = 69\%,\, p < .01\).

Likewise, paternal smoking was also associated with the increased risk of depression in the meta-analysis of four studies \((OR = 1.28; 95\%\, CI: 1.11–1.48, k = 4, N = 26,237)\) (Menezes et al., 2013; Taylor et al., 2017). There was no evidence of heterogeneity between studies \(I^2 = 33\%,\, p = .21\). Visual assessment of funnel plots, and Egger as well as Begg tests provided no evidence of obvious publication bias for maternal smoking exposure and paternal smoking exposure.

In contrast, the qualitatively analyzed studies \(k = 4\) were largely unsupportive of a relationship between maternal smoking and offspring depression. One study reported significant associations across all trimesters \(r_{1st\, trimester} = .07, p < .10; r_{2nd\, trimester} = .07, p < .10; r_{3rd\, trimester} = .06, p < .10\) (Gray et al., 2005), but three other studies found no association (Fergusson et al., 1998; Leung et al., 2015; Liu et al., 2011).

Maternal drinking. The meta-analysis did not find a statistically significant association between mothers’ drinking habits and depression among two studies \((OR = 1.09; 95\%\, CI, 0.96–1.24, k = 2, N = 13,976)\) (Kingsbury et al., 2016; Levine, 2014), and there was no evidence of heterogeneity between studies \(I^2 = 0\%,\, p = .47\). No obvious publication bias was observed from visual assessment of a funnel plot nor Egger/Begg test.

Qualitatively analyzed studies \(k = 3\) suggest a potential link between maternal drinking and offspring depression, with two qualitatively analyzed studies reporting that exposure to maternal drinking increased the risk of depression and depressive symptoms in offspring (Gray et al., 2005; O’Connor & Kasari, 2000); however, another study reported no association between maternal drinking (defined as \(>1\) drink per day) and offspring depression (Betts, Salom, et al., 2015).

Famine. One Chinese study found that exposure to famine in utero increased the risk of depression among offspring (Li et al., 2018).

For the meta-analysis

Publication bias. We used Begg and Egger tests to explore publication bias. Most of the studied variables did not have publication bias. The shapes of the funnel plots did not indicate any evidence of obvious asymmetry (see Figure S1). Although Begg test found no significant publication bias for all the exposures, the results of Egger test suggested that two variables (birth order and maternal prenatal depression) had publication bias (Table S6). The trim and fill method was then used to recalculate the pooled results for these two variables. The adjusted pooled effect of birth order exhibited a similar trend \((OR = 0.99; 95\%\, CI 0.84–1.18)\) with three potential studies were filled. For prenatal depression, the adjusted pooled effect became non-significant \((OR = 1.21; 95\%\, CI 0.90–1.55)\) after two additional studies were added.

Sensitivity analysis. Each study was excluded at one time to test the stability of the pooled results. We found that findings of three variables (SGA, parental age greater than 35 years, and paternal smoking)
changed when we removed one study at a time. The rest of the results remained unchanged (see Figure S2). Subgroup analyses were also utilized for prenatal, perinatal, and postnatal exposures. Subgroup analyses supported that the effects of prenatal, perinatal, and postnatal exposures on depression all remained significant (see Figures S3a and S3b).

**Discussion**

This review provides the first comprehensive overview of prenatal, perinatal, and postnatal exposures related to offspring’s depression. These early-life exposures cover biological, psychological, and sociological characteristics that are pertinent for depression. A total of 28 prenatal, perinatal, and postnatal exposures had been reported on in the 64 prospective cohort studies, we provide both quantitative and qualitative syntheses. For the quantitative synthesis, our meta-analysis identified that a total of 12 prenatal and perinatal/postnatal factors were associated with an increased risk of depression. These factors were low birth weight, premature birth, small gestational age, having teen birth parents (<20 years old), having birth parents older than 35 years, maternal education, SES, paternal smoking, maternal smoking, maternal stress, maternal anxiety, and maternal prenatal depression. The qualitative syntheses identified a total of 23 factors (some overlapped with quantitative analysis) and were generally supportive of the relationships between some of the risk factors identified in the meta-analysis and offspring’s depression. The qualitative analysis also provided additional information on other risk factors that may influence offspring’s depression. Together these studies provided solid evidence for a developmental origin of depression hypothesis.

For the biological factors that are studied in this review, our findings are generally consistent with previous reviews on specific biological factors. For example, a previous systematic review of 14 studies reported a positive association between low birth weight and depression, but not for premature birth and SGA (Loret de Mola, de Franca, Quevedo Lde, & Horta, 2014). They noted that conservative analytical approaches and publication bias might confound the relationships between premature birth, SGA, and depression. Our findings on low birth weight and depression are consistent with the literature. Another meta-analysis also reported a small but significant effect of low birth weight on depression (Wojcik, Lee, Colman, Hardy, & Hotopf, 2013). These associations of birth outcome measures (low birth weight, SGA, and premature birth) can be potentially explained by the glucocorticoid programming of the hypothalamic–pituitary–adrenal axis (HPAA) (Seckl & Meaney, 2004). Preterm and SGA births were linked with altered HPAA activity in an early acquired and persisting neuro-physiological vulnerability (Patton, Coffey, Carlin, Olsson, & Morley, 2004), which then becomes involved in the development of depression due to an increased sensitivity to adversity (Räikkönen et al., 2008). Low birth weight may be related to an increased level of circulating glucocorticoids. Other hormonal systems like growth hormone – insulin-like growth factor system, can synergize HPAA to regulate the fetal growth and brain development and may contribute to the pathogenesis of depression (Russo, Gluckman, Feldman, & Werther, 2005). These birth measures are also related to the activity of placental enzymes, which regulate maternal-fetal glucocorticoid and serotonin transfer. These enzymes are known as key modulators of fetal programming in adult mental disorders (Bonnin & Levitt, 2011). Neurological damage caused by preterm births, such as cerebellar hemorrhagic injury, has been related to internalizing behavioral problems (Limperopoulos et al., 2007). We found no association between birth order and subsequent depression. The literature on birth order and depression is mixed (Carballo et al., 2013; Hardt, Weyer, Dragan, & Laubach, 2017). The relationship between birth order and depression needs to consider the presence of different family sizes, spacing between offspring, the underlying perceptions adolescents had of their older sibling, or support levels within the sibling dyads (Finan, O’hanessian, & Gordon, 2018).

There has been an increasing interest in the relationship between parental age and psychiatric disorders (Chudal et al., 2014; D’Onofrio et al., 2014). We found both younger parents (<20 years) and older parents (>35 years) were more likely to have depressed children. This is consistent with prior reviews on autism and psychotic disorders (Lopez-Castroman et al., 2010; Sandin et al., 2012). Younger parents are more likely to be challenged by unplanned parenting, stress, marital discord, lack of parenting experience, and economic circumstances, which in turn affect the trajectory of normal development of their children (Kessler et al., 2010). Older parents may be also unprepared for the relationship and life changes brought by the advent of a child.

Our review found that the studied psychosocial factors (maternal stress, anxiety, and prenatal depression) were related to depression in offspring. Depression, stress, and anxiety during pregnancy can trigger increased levels of maternal glucocorticoids, which have been considered as the key connection linking maternal adversity to the fetus (McGowan & Matthews, 2018; Stroud et al., 2016). Evidence has also shown that maternal glucocorticoids increase the risk of children psychopathology (Buss, Davis, et al., 2012). Also, depression is somewhat heritable (Agrawal, Jacobson, Gardner, Prescott, & Kendler, 2004). Maternal stress and
prenatal anxiety may be associated with less optimal development trajectory for offspring (Pesonen, Räikkönen, Strandberg, & Järvenpää, 2005). Genetic susceptibilities combine with early-life environmental adversities can pose a threat to a normal growth and development.

Empirical psychological and social studies have stressed the importance of the timing of exposures, that is, the period of development in which the infant may be more susceptible to the effects of these exposures (Michel & Tyler, 2005; Sanger, Iles, Andrew, & Ramchandani, 2015). For example, studies have shown that the activation of the maternal stress response especially during the second and third trimesters, including glucocorticoid signaling and the immune response, could damage offspring’s brain development (Wang, Kloth, & Badura, 2014). Maternal depression in the early postnatal months has been found to be closely related to child development (Rigato, Stets, Bonneville-Roussy, & Holmboe, 2020). Maternal depression may not have a single sensitive period but instead has a cascading influence and cumulative impact across the whole pregnancy period and into early childhood (Bagnar, Pettit, Levinsohn, & Seeley, 2010).

Although prenatal depression was seen as the strongest predictor of postnatal depression and may persist into the postnatal period (Heron, O’Connor, Evans, Golding, & Glover, 2004), in this present review we also observed that maternal prenatal depression was an independent risk factor for offspring’s depression and the contributing role of maternal prenatal depression in offspring’s depression was diminished. Therefore, we could propose that the effect of prenatal depression in offspring’s depression is independent from the effect of postnatal maternal depression in offspring’s depression. Some supporting evidence has been found which demonstrated that there is generally no effect of change in maternal depression from the prenatal to postnatal period with the effect of postnatal depression limited to mothers with lower education (Pearson et al., 2013). These findings suggest that prenatal and postnatal maternal depression may affect offspring via different pathways. Prenatal depression might exert a detrimental effect on utero through biological mechanisms (Srinivasan, Pearson, Johnson, Lewis, & Lewis, 2020). A great deal of physiological changes of depressed mothers during pregnancy posit an adverse intrauterine environment which can alter fetal developmental programming (Wen et al., 2017). In contrast, postnatal depression impacts offspring possibly through environmental factors such as parental discipline and social engagement which predict increased vulnerability to psychopathology in offspring (Murray, 2009). Depressed mothers have been found to be less sensitive in responding to and interacting with their children, and more likely to have unpredictable parenting styles (Milgrom, Westley, & Gemmill, 2004). Therefore, it is suggested there is no direct effect of postnatal depression on offspring, but its effect is possibly mediated through the pathways of the home environment (Pearson et al., 2013).

For sociological characteristics, lower SES and lower maternal education were associated with an increased risk in subsequent depression in children. Consistent with our findings, a previous systematic review of 55 studies reported that children from socioeconomically disadvantaged families were at a higher risk of mental health problems. This meta-analysis also found that low parental education was the strongest risk factor for mental disorders among children and adolescents (Reiss, 2013). Children from low SES families, especially for those with parents of having lower levels of education, have limited access to the material, psychological, and social resources that model important contributions to the development of positive mental health (McLaughlin et al., 2011).

Maternal smoking and paternal smoking were associated with an increased risk of offspring’s depression in the current meta-analysis. One of the explanations is the ‘fetal programming hypothesis’, which hypothesizes that the developmental origin of psychiatric disorders might be a result of prenatal exposure to adverse intrauterine conditions such as infection, pollution, smoking, and other substance use, altering the body’s organs and systems (Buss, Entringer, & Wadhwa, 2012). Stroud and his colleague highlighted an important role of placental serotonin signaling in modulating prenatal programming of the fetal HPA axis by maternal adversity (Stroud et al., 2016). More importantly, we observed a slightly stronger maternal-offspring association compared with paternal-offspring association for smoking exposures during pregnancy. We anticipate that there is a causal intrauterine effect between smoking and depression in offspring rather than a link due to genetic and shared environmental confounders. If the genetic and shared environmental confounders accounted for this association, the magnitude of the association between maternal and paternal smoking and depression in offspring would be similar (Langley, Heron, Smith, & Thapar, 2012; Richmond, Al-Amin, Smith, & Relton, 2014). The possible explanations to account for the differential effects of maternal and/or paternal smoking on the fetus are the unique maternal utero effects come through causal pathways affecting fetal programming (Taylor et al., 2017). Future studies (e.g., family-based sibling control studies), which partially account for genetic and environmental confounders, are needed to reveal the nature of the relationship between parental smoking and offspring’s depression.

This review provides the first comprehensive overview of prenatal, perinatal, and postnatal factors associated with offspring’s subsequent depression. This review used a comprehensive search and
followed the recommended guidelines for reporting of results and methodological quality assessment to ensure the findings objectively summarize the literature on the DOHaD in depression. This review only included prospective cohort studies, good quality studies, studies with large sample sizes, with relatively long and adequate follow-up periods, with reliable measurements of exposures and outcomes to deliver robust evidence on developmental origins of depression.

However, several potential limitations should be noted. First, 2 of the 16 factors in the meta-analysis (birth order and prenatal depression) have publication bias. The pooled estimate of prenatal depression became nonsignificant after taking two additional studies (as suggested by trim and fill tests) into account. Interpretation of the relationship between prenatal depression and offspring's depression warrants attention. Second, we observed high heterogeneity for a few exposures and the limited number of studies in some exposures precluded the detailed subgroup analyses. Also, even though 33 studies were included in the overall meta-analysis, for some exposures there were generally fewer than six studies included, thus limiting the statistical power to detect heterogeneity and to assess potential effect modification caused by study characteristics. Third, although we used subgroup analysis, sensitivity analysis, and meta-regression analysis to explore potential confounders involved in the relationship between prenatal, perinatal, and postnatal factors and depression, there are still other unknown and unobserved confounders that might also be involved in this relationship. Both measured and unmeasured familial confounders can influence the parent–child relationship. Kingsbury et al. (2016) reported that neither maternal drinking nor maternal prenatal depression was associated with offspring depression after controlling for sex, ethnicity, maternal teen status, maternal education, maternal history of depression, prenatal smoking, or alcohol use, prenatal depression or anxiety, high maternal stress at 8 months postpartum, and maternal depression at 8 years postpartum. A Swedish study found that there was no clear evidence to support the association between maternal smoking during pregnancy and offspring depression in a sibling-controlled analysis with the same family context and genetic predisposition (Taylor et al., 2017), though there are limitations in using sibling controls. Fourth, meta-analysis cannot take all studied covariates from original studies into account because of variations in what were measured across the included studies. We used sensitivity and subgroup analysis instead to explore potential confounders that might be involved in the relationship between offspring’s depression and prenatal, perinatal, and postnatal exposures.

Conclusion

This systematic review provides a robust and comprehensive overview of prenatal, perinatal, and postnatal factors associated with the risk of offspring’s depression. Within the framework of the biopsychosocial model, a total of 12 prenatal and perinatal/postnatal factors among 28 studied factors were significantly associated with offspring’s depression in the meta-analysis. The findings of the review highlight the need for clinical and public health interventions to focus on these identified risk factors. Large prospective cohort studies are warranted to investigate the combined effects of co-existing early-life exposures.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Figure S1. Funnel plot for the analysis of in utero and perinatal factors and depression risk.
Figure S2. Sensitivity analyses for the association between in utero and perinatal factors and depression risk.
Figure S3a. Subgroup meta-analysis of the relationship between prenatal factors and offspring's depression.
Figure S3b. Subgroup meta-analysis of the relationship between perinatal/postnatal factors and offspring's depression.
Table S1. MOOSE checklist for meta-analyses of observational studies.
Table S2. Characteristics of included studies on in utero, perinatal and postnatal exposure, and depression risk.
Table S3. A summary of the Newcastle–Ottawa Scale (NOS) quality assessment for selected studies.
Table S4. Meta-regression analyses.
Table S5. Detailed findings from qualitative studies.
Table S6. Publication bias for the included studies.
Appendix S1. Search strategies.

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Key points

- This systematic review provides the first overview that comprehensively synthesizes the effects of prenatal, perinatal, and postnatal attributes on offspring’s depression.
- Low birth weight, premature birth, small gestational age, maternal education, socioeconomic status, having young parents (~20 years), having older parents (~35 years), maternal smoking, paternal smoking, maternal stress, maternal anxiety, and maternal prenatal depression significantly increased the risk of depression among offspring.
- The qualitative analysis generally provides support for the meta-analysis findings and adds information on a range of additional risk factors influencing depression in offspring.
- Findings of this review highlight the need for clinical and public health interventions to focus on these identified risk factors. Large prospective cohort studies are warranted to investigate the combined effect of co-existing early-life exposures.

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