# Considering Environmental Toxicants as Risk Factors for Postpartum Depression: A Systematic Review

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## ABSTRACT

Postpartum depression is a serious mental illness with onset of symptoms appearing anytime within the first four months after delivery (e.g. irritability, severe sadness, profound feelings of hopelessness, etc.). Environmental toxicants are synthetic (i.e. manufactured) or naturally found chemicals that are not produced by organisms as a result of cellular metabolism (e.g. tobacco smoke, pesticides, etc.). There is limited consideration for how exposure to environmental toxicants can create adverse psychological health effects, specifically postpartum depression. The purpose of this systematic review was to determine if the literature supports a link between exposure to environmental toxicants during the prenatal/perinatal period and postpartum depression and if so, to identify whether there are specific classes of toxicants that provide a higher risk for postpartum depression. Several databases were used to search the online literature, with the following inclusion criteria: articles published in English, publication years between 1995-2018, and with women of reproductive age (15-49 years old). The article selection process comprised of screening each article by title/abstract, followed by screening those articles based on full-text. Six categories of toxicants were identified among the thirty included articles. Active/passive smoke exposure was largely found to increase the risk of developing postpartum depression; dietary supplements provided mixed results; antidepressants demonstrated preventative effects; particulate air pollution was found to be associated with postpartum depression; oral contraceptives (DMPA) exhibited an increase in postpartum depressive symptoms; and organochlorine pesticides had no associative risk. Quality assessments were performed for all of the included articles, with the majority being assessed as satisfactory. This systematic review presents as a foundation for encouraging future research to investigate the link between environment and mental health, in order to attain a greater perspective.



Keywords: postpartum, depression, environment, toxicants, xenobiotics, prenatal, perinatal, exposure

# RÉSUMÉ

La dépression post-partum est une maladie mentale sérieuse dont les symptômes peuvent apparaitre lors des quatre premiers mois suivant l'accouchement (par ex. irritabilité, tristesse importante, sentiments profonds de désespoir, etc.). Les substances toxiques provenant de l'environnement sont des produits chimiques synthétiques (c'est-à-dire fabriqués) ou naturels qui ne sont pas produits par des organismes en raison de leur métabolisme cellulaire (par ex. fumée de tabac, pesticides, etc.). Il y a peu de considération en ce qui est d'un lien entre l'exposition à ces substances environnementales et leurs effets sur la santé psychologique d'un individu, en particulier le lien avec la dépression post-partum. L'objectif de cette étude systématique était de déterminer si la littérature confirme l'existence d'un lien entre l'exposition à des substances environnementales toxiques lors de la période prénatale ou périnatale avec la dépression post-partum. De plus, s'il y a un lien, nous nous intéressions à déterminer s'il existe des catégories spécifiques de substances toxiques qui présentent un risque plus élevé pour la dépression post-partum. Plusieurs bases de données ont été recherchées pour la littérature pertinente, avec les critères d'inclusion suivants : articles publiés en anglais, années de publication entre 1995 et 2018, et études portant sur les femmes en âge de reproduction (15-49 ans). Le processus de sélection des articles comportait la sélection d'articles par titre/résumé, suivit d'une sélection approfondie parmi ces articles par la lecture du texte intégral. Six catégories de substances toxiques ont été identifiées parmi les trente articles inclus. On a découvert que l'exposition active/passive à la fumée augmentait largement le risque de dépression post-partum ; la prise de suppléments alimentaires a donné des résultats variés ; les antidépresseurs ont démontré des effets préventifs envers la dépression post-partum; la pollution atmosphérique particulaire a été associée à la dépression post-partum ; les contraceptifs oraux (DMPA) ont démontré une augmentation des symptômes dépressifs post-partum ; les pesticides organochlorés n'ont pas démontré de risque. Une évaluation de la qualité des études a été effectuée pour tous les articles inclus; la majorité ont été jugées comme étant de qualité satisfaisante. Cette étude systématique sert d'une base d'encouragement aux recherches futures qui exploreront le lien entre l'environnement et la santé mentale, afin d'y obtenir une meilleure perspective.



Mots-clés : post-partum, dépression, environnement, substances, toxiques, prénatale, périnatale, l'exposition

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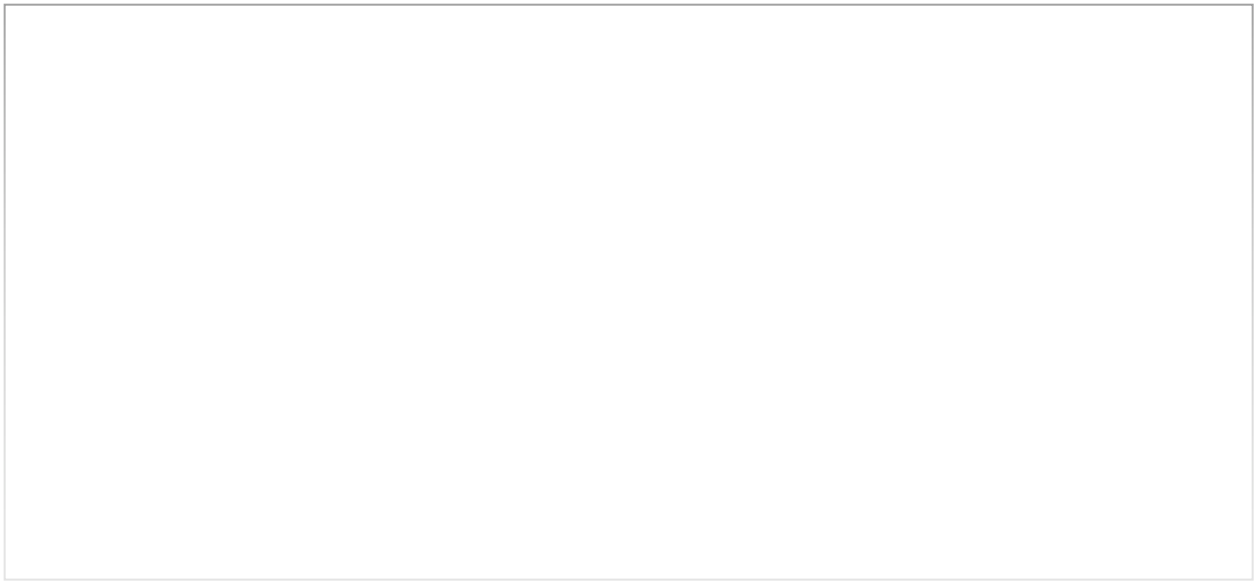
**Abbreviations**

AGRO: Agrochemicals
ACS: American Chemical Society
ADS: Antenatal depressive symptoms
ADHD: Attention deficit hyperactivity disorders
ASD: Autism spectrum disorder
BDI-II: Beck's Depression Inventory II
B-HCH: beta-Hexachlorocyclohexane
BPA: Bisphenol A
CEPA: Canadian Environmental Protection Act
CMP: Chemicals Management Plan
CASP: Critical Appraisal Skills Programme
DDT: Dichlorodiphenyltrichloroethane
DMPA: Depot medroxyprogesterone acetate
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
DSHEA: Dietary Supplement Health and Education Act
DHA: Docosahexaenoic acid
EPDS: Edinburgh Postnatal Depression Scale
EPA: Eicosapentaenoic acid
ENVR: Environmental Chemistry
GAD: Generalized anxiety disorder
GHSP: Global Horizon Scanning Project
HAM-D: Hamilton Rating Scale for Depression
IUD: Intrauterine device
NDD: Neurodevelopmental disorder
OCP: Organochlorine pesticide (OCP)
$PM_{2.5}$: Particulate matter with diameter </= 2.5 μm
POP: Persistent organic pollutant
PCB: Polychlorinated biphenyl
PDS: Postpartum depression symptoms
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
AQS: Protection Agency Air Quality System
RCT: Randomized-controlled trial
SHS: Second-hand smoke
SSRI: Serotonin reuptake inhibitors
SETAC: Society of Environmental Toxicology and Chemistry
THS: Third-hand smoke
VOC: Volatile organic compound

# Chapter 1: Introduction



### I) Postpartum Depression

Depression is among the most disabling disorders for women in their childbearing years (O'Hara, 2009). Childbirth represents a time of great vulnerability for women to become mentally unwell, with postpartum depression representing the most frequent form of maternal morbidity after delivery (Stocky & Lynch, 2000). Postpartum depression is a serious mood disorder affecting 10-13% of women worldwide with symptoms such as depressed mood, loss of interest and enjoyment, and reduced energy leading to diminished activity (World Health Organization, 2015).

Postpartum affective disorders are typically divided into three categories: postpartum blues, postpartum depression, and puerperal (postpartum) psychosis (Robertson et al., 2004). Postpartum blues or "baby blues" are a transient state of heightened emotional reactivity that occurs in approximately 50% of women who have recently given birth (Miller, 2002). Women with postpartum blues cry more easily than usual, are more irritable, and are more emotionally

labile than usual (Miller, 2002). Symptoms typically begin three to four days after delivery and most often resolve by day 10 (Seyfried & Marcus, 2003). Postpartum [nonpsychotic] depression occurs in approximately 10-20% of women within 6 months of delivery (Miller, 2002). Postpartum depression is characterized by low mood and sadness accompanied by anhedonia, impaired concentration, disrupted sleep and appetite, psychomotor disturbance, feelings of worthlessness or guilt, social withdrawal, and recurrent suicidal ideation (Meltzer-Brody et al., 2018). There has been some debate over the phenomenology of postpartum depression as compared to depression not relating to childbearing (Seyfried & Marcus, 2003). Major depressive disorder with peripartum onset is defined in the DSM-V as the most recent major depressive episode occurring during pregnancy as well as within the four weeks following delivery (Segre & Davis, 2013; American Psychiatric Association, 2013). In major depressive disorder with postpartum onset, anxiety symptoms are more prevalent than in major depressive disorder occurring at other times (Bernstein et al., 2008). Postpartum (or puerperal) psychosis is the most severe and uncommon form among postnatal affective illnesses, with rates of 1-2 episodes per 1000 deliveries (Robertson et al., 2004). Symptom presentation can be dramatic: full-blown delusions, hallucinations, bizarre behaviour, mania, depression, perplexity, confusion, lability and other affective symptoms can develop within days to weeks of childbirth (Heron et al., 2008). Many researchers agree with the idea that postpartum psychosis is a psychotic episode triggered by the complex psychosocial stressor and hormonally-related changes that occur following childbirth (Seyfried & Marcus, 2003). The short-term prognosis for postpartum psychosis is generally good, however, women need to be counselled about the risks they run of a further puerperal or non-puerperal episode (Florio, Smith, & Jones, 2013). This will include discussing the need for longer-term mood stabilising medication and other measures, given the

high risk of recurrence following further deliveries (Florio et al., 2013). Among the types of postpartum affective disorders, postpartum depression will be the primary study outcome considered for this systematic review.

**a) Risk factors**

The risk factors associated with developing postpartum depression have been extensively reported and identified in the literature and these factors can be characterized as biological or psychosocial. Biological factors which have consistently been found to be associated with an increased risk of postpartum depression include: family history of depression, a past history of depression or premenstrual dysphoric disorder, and experiencing depressed mood or anxiety during pregnancy (Robertson et al., 2004). Psychosocial factors which have been consistently found to predict postpartum depression include: experiencing stressful life events, domestic violence, and lack of perceived social support (Miller & LaRusso, 2011). Several other factors, including low socioeconomic status, low self-esteem (particularly in relation to parenting ability), unplanned or unwanted pregnancy, negative birth experience or obstetric complications, as well as difficult infant temperament, have all been less consistently demonstrated to be risk factors for developing postpartum depression – but have been identified nonetheless (Miller & LaRusso, 2011).

In the majority of cases, postpartum depression is self-limiting and could resolve within months of onset; however, for many women, childbirth can be the stressor that triggers the start of recurrent or chronic episodes of the depressive disorder (Roberston et al., 2004). The current evidence shows that untreated maternal depression can have serious and long-lasting effects: they range from a general negative impact on the child, the partner, and other family members to the danger of an increased risk of recurrence, suicidality of the mother, threat to the bonding

between mother and child, as well as physical, cognitive, emotional, and social developmental disorders in the children (Schipper-Kochems et al., 2019). Although all women are susceptible to postpartum depression, it is possible for physicians and healthcare professionals to identify women at higher risk for closer follow-up and intervention when necessary (Roberston et al., 2004).

**II) Environmental Toxicology**

Environmental toxicology is a multidisciplinary field of science focused on studying the dangerous effects of various chemical, biological, and physical agents on living organisms. Toxicants are synthetic (i.e. manufactured) or naturally found chemicals that are not produced by organisms as a result of cellular metabolism (e.g. arsenic) (Belson, Schier, & Patel, 2005). Environmental toxicants can be encountered in a variety of indoor and outdoor locations, via different routes of exposure. The following toxicants can be encountered in either indoor or outdoor settings: carbon monoxide, tobacco smoke, molds/biologic pollutants, lead/heavy metals, pesticides/disinfectants, methylmercury, plasticizers (BPA and phthalates), solvents, and asbestos (Falck et al., 2015). Routes of exposure can include inhalation, such as dust or fumes; ingestion, such as, of pesticide residues on fruits and vegetables; and dermal absorption, such as, of ultraviolet-B radiation from the sun or direct skin contact with corrosive household cleansers (Pope, Snyder, & Mood, 1995).

**a) Environmental toxicants**

The environmental toxicants previously identified are those of major interest for the purposes of this review and are further elaborated throughout this chapter.

Environmental tobacco smoke contains more than 250 harmful chemicals, including nicotine, carbon monoxide, formaldehyde, etc., consists of sidestream smoke from the end of a burning cigarette, and mainstream smoke (or second-hand smoke) exhaled from the smoker's lungs (Hoh et al., 2012).

Heavy metals are considered any metallic element that has a relatively high density and is toxic or poisonous even at low concentration (Duruibe, Ogwuegbu, & Egwurugwu, 2007). Heavy metals include lead, cadmium, zinc, mercury, arsenic, silver, chromium, copper, iron, and the platinum group elements (Duruibe et al., 2007). Sources of exposure occur from inhalation, ingestion, and handling of contaminants, via common sources such as food, drinking water, motor vehicle emissions, and contaminated household products (Falck et al., 2015). These heavy metals are present in our everyday environment because they are present in many industrial products used in homes such as household disinfectants, nickel/cadmium batteries, artist paints, mirror coatings, wine bottle wraps, old paints and tiles, and linoleum amongst others (Duruibe et al., 2007).

Lead is a naturally occurring heavy metal that is found in the Earth's crust, however, much of the lead in the environment is a result of human activities such as manufacturing, mining, and burning fossil fuel (Meadows-Oliver, 2012). Mercury is also a naturally occurring element released into the environment; once released, bacteria can convert elemental mercury into methylmercury, which then can make its way through the food chain, is often bioaccumulated and can eventually makes its way to humans (Meadows-Oliver, 2012). Routes of exposure for both lead and mercury may occur through inhalation, ingestion, or through dermal contact (Meadows-Oliver, 2012).

Pesticides are a broad group of chemicals intended to kill unwanted insects, plants, molds, and rodents and they are often used in vicinity of households (residential use is common), schools, and in agriculture (Falck et al., 2015). Many pesticides are readily absorbed through skin, and inhalation can occur from lawn and agricultural sprays (Falck et al., 2015); note that exposure also occurs via food exposure, for example pesticide residues on fruits and vegetables (Pope et al., 1995).

Bisphenol A (BPA) is used in the production of plastic bottles and as a protecting coating inside metal cans to improve rigidity; the primary source of exposure is via ingestion of food and beverages (Falck et al., 2015). Phthalates are a family of industrial chemicals that have been used for a variety of purposes: they are added to plastics in the manufacture of children's toys and medical devices to make them soft and flexible as well as to cosmetics as a vehicle for fragrance (Jurewicz, Polańska, & Hanke, 2013). Phthalates are also found in adhesives and glues, agricultural adjuvants, building materials, personal care products, detergents, food products and textiles (Jurewicz et al., 2013). Like BPA, the primary source of exposure to phthalates is via ingestion as they both can leach from plastic containers into food and beverages, particularly after heating (Falck et al., 2015). Since phthalates are ubiquitous in daily life, the potential consequences of human exposure to phthalates have raised concerns in the general population and have been further studied in susceptible subjects such as pregnant women, infants, and older children (Api, 2001).

Persistent organic pollutants (POPs) are man-made chemicals and include a group of diverse substances such as polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs), that are resistant to biodegradation and ubiquitously present in our environment (Dirinck et al., 2014). Humans are predominantly exposed through the consumption of contaminated food,

primarily meat, fish, and dairy products (Dirinck et al., 2014). Volatile organic compounds (VOCs) are hydrocarbons which are emitted as gases from certain solids or liquids and can therefore be considered as air pollutants (Falck et al., 2015). Levels of VOCs can be 5-10 times higher indoors than outdoors and most notable indoor sources include solvents, floor adhesive, paint, cleaning products, furnishings, polishes, and room fresheners (Rumchev et al., 2004).

Solvents are lipophilic volatile organic compounds that have the ability to dissolve a large array of materials (Glass et al., 2015). They include compounds such as benzene, isopropanol, toluene, xylene, and other aromatic hydrocarbons and chlorinated solvents such as methylene chloride (Dick, 2006). Organic solvents are so widely used in the modern world as they are employed in paints, pharmaceuticals, adhesives, printing inks, pesticides, cosmetics, and household cleaners (Dick, 2006).

**b) Considering additional substances**

In addition to these environmental toxicants, there is the consideration of the 'environment' to be defined as 'any external exposure to substances.' This continued definition of 'environment' for this systematic review allows for the inclusion of articles which discuss other types of substances women may be exposed to in their perinatal environment such as antidepressants, dietary supplements, and oral contraceptives. The word 'toxicants' is used to mean xenobiotics in general, but those with the potential to cause harm, specifically toxic effects.

The focus of this research was expanded to include prenatal and/or perinatal exposure to those additional substances as potential risk factors for the development of postpartum depression. Antidepressants (ex: sertraline and nortriptyline) are a type of prescribed medication primarily used to treat clinical depression. A significant number of pregnant women use antidepressants with estimates from 4-10% in different populations and the majority of these

women are being treated with selective serotonin reuptake inhibitors (SSRIs), however the use of newer antidepressants is increasing (Pedersen, 2017). The relative safety of such medication, for example, selective-serotonin reuptake inhibitors (SSRIs), has led to their widespread use to treat depressive disorders in women of childbearing age, despite knowledge regarding the risks of prenatal exposure to SSRI medication remains far from complete (Casper et al., 2011). The majority of these health risks mentioned in the literature have been largely centered on resulting neonatal developmental outcomes, while minimal research mentions potential adverse maternal health outcomes with prenatal and perinatal exposure to this type of medication (Dubovicky, Belovicova, Csatlosova, & Bogi, 2017).

Women may also take dietary supplements (for example, omega-3 fatty acids) before/during their pregnancy, in order to meet their extra nutritional needs. As defined by the U.S. Congress in the Dietary Supplement Health and Education Act (DSHEA), a dietary supplement is a product that: 1) is intended to supplement the diet, 2) contains one or more dietary ingredients (including vitamins, minerals, herbs, or other botanicals, amino acids, and other substances) or their constituents, 3) is intended be taken by mouth as a pill, capsule, tablet, or liquid, and 4) is labeled on the front panel as being a dietary supplement (Schweitzer, 2006). The interest in including these supplements as 'external environmental toxicant exposure' is based on the notion that certain nutritional deficiencies such as low levels of DHA (docosahexaenoic acid, an omega-3 fatty acid) found in seafood, calcium, B vitamins, vitamin D, and iron have been investigated in relation to postpartum depression but so far this research has been inconclusive (Miller, 2002). Although, research studies have presented conclusive evidence that women have been found to be depleted in omega-3 polyunsaturated fatty acids during

gestation and breastfeeding as there is preferential diversion of omega-3 fats to the baby (Huang, et al., 2013). An assumption can be concurred from this finding, in that pregnant women would be encouraged and feel more inclined to consume dietary supplements, such as omega-3 fatty acids, in order to compensate for this nutritional depletion. Given that these supplements could be beneficial in improving nutritional health during the perinatal period, there should also be consideration for the further exploration as to whether these supplements could in turn affect maternal mental health.

Hormonal birth control includes estrogen-progesterone combined hormonal contraception, which can provide effective protection against pregnancy with many non-contraceptive health benefits and can safely be used by most women (Lauring et al., 2016). Oral contraceptives regulate the changes in hormone levels during a woman's cycle by using different forms of synthetic hormones that mimic the estrogen and progesterone that is naturally produced in a woman's body ("Hormonal Contraception", 2018). There are many different types of estrogens and progestins, and different types of pills contain different combinations, though their mode of action is similar (Jin, 2014). Postpartum contraception is used to prevent unintended and closely spaced pregnancies in the first twelve months after giving birth (Singhal et al., 2014). Some types of contraception can be used immediately after delivery; however, it is recommended to use progestin only methods, which research shows has no effect on breast milk volume, or on infant-growth (Singhal et al., 2014).

**III) The Importance to Consider Environmental Risk Factors**

The link between adverse health effects and exposure to environmental hazards has been well documented in the literature. However, there is limited consideration for how exposure to environmental toxicants can create adverse psychological health effects. Various research studies

have focused on investigating the link between environmental toxicants and other areas of mental health, in particular neurodevelopmental disorders (NDDs). Taken together, these notions serve as the underlying rationale for this systematic review, that is, in the determination of what has been reported in the literature in terms of exposure to environmental toxicants and maternal mental health, with a focus on conditions such as postpartum depression.

Heyer and Meredith (2017) highlighted that although NDDs are known to have a genetic component, it is increasingly evident that disturbances to the developing nervous system may be caused by exposure to non-genetic, environmental factors. Through a comprehensive literature review involving human epidemiological and animal experimental studies, these authors were able to identify developmental periods for increased vulnerability to environmentally-modifying compounds and determine whether and how exposure during these specific periods of time could increase the risk for the NDDs of autism, attention deficit hyperactivity disorder (ADHD), or schizophrenia (Heyer & Meredith, 2017). Their report states that many environmental toxicants have distinct sensitive time periods during which exposure may disrupt critical developmental events, thereby increasing the risk of developing NDDs - the primary finding being that the majority of these time periods occur prenatally, rather than postnatally (Heyer & Meredith, 2017). The discovery from this study highlights the importance of preventing prenatal exposure to environmental toxicants, in order to reduce the likelihood and prevalence of adverse mental health effects. However, this study's focus is primarily on the offspring's health and not that of the mother - thus, there needs to be more consideration for how exposure to these hazardous substances could impact maternal health as well, more specifically, maternal mental health.

An area of research which is most noteworthy, is the growing body of evidence documenting an association between second-hand smoke exposure and mental health outcomes.

Bandiera and colleagues (2011) explored this association in their study which examined biologically confirmed second-hand smoke exposure and symptoms among a variety of mental health disorders of the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) using a nationally representative sample of children and adolescents in the United States. Second-hand smoke exposure was measured by level serum cotinine levels (a metabolite of nicotine) with a level of 3 ug/L or higher being the cut-off point to distinguish smokers from current non-smokers (Bandiera et al., 2011). The DSM-IV symptoms were identified based on derived information on mental disorders from the National Institute of Mental Health Diagnostic Interview Schedule for Children Version IV (DISC-IV), a structured questionnaire administered by lay interviewers to ascertain 12-month diagnostic criteria for DSM-IV conditions in children and adolescents (Bandiera et al., 2011). Symptoms of each mental disorder were reported based on various score ranges (e.g. MDD (major depressive disorder) child report score range 0-21; ADHD (attention deficit disorder) child report score range 0-23, etc.). The main finding from this study indicated that serum cotinine levels were positively associated with symptoms of MDD, GAD (generalized anxiety disorder), ADHD, and conduct disorder (Bandiera et al., 2011). Furthermore, there were sufficient positive cases for the diagnosis of ADHD and conduct disorder (Bandiera et al., 2011). This study is among many others which continue to investigate and further the understanding that second-hand smoke exposure and poor mental health conditions is a major public health problem among children and adolescents. The findings from this study support the expanding amount of research investigating the association between various substances and hazards present in the environment and the development of mental health disorders among varying populations. Again, the target population of this study were children and adolescents and with these findings, it's possible to concur that exposure to environmental

toxicants such as tobacco (through second-hand smoke) can cause adverse mental health effects among this young population. Nonetheless, more research needs to investigate how this exposure could have similar mental health effects on another significant study population - women of childbearing age in their perinatal stages of gestation.

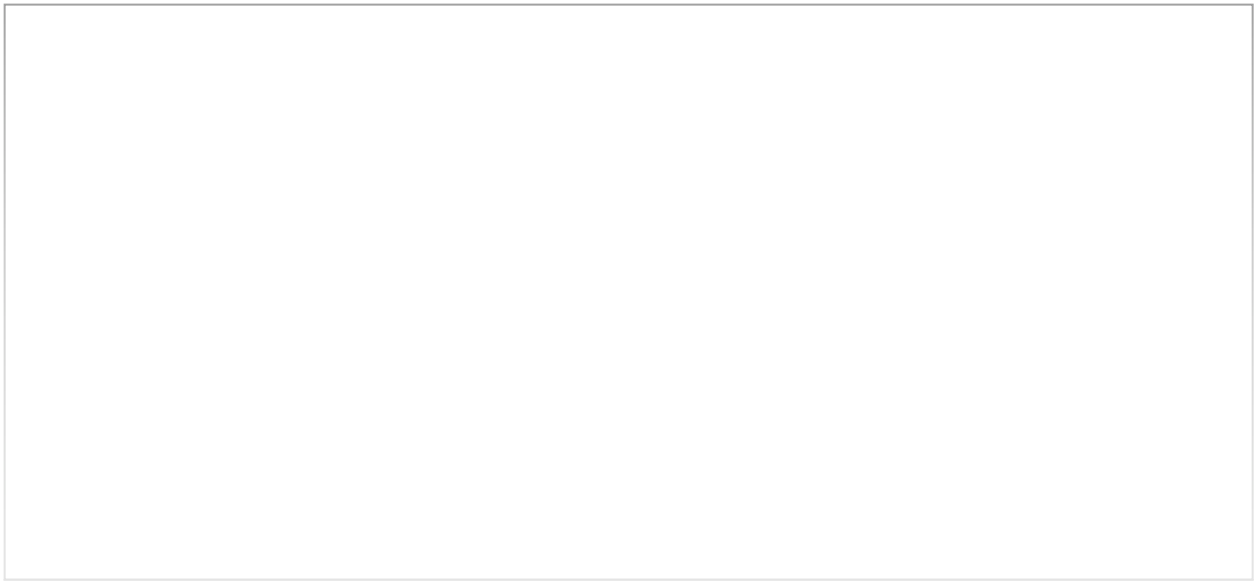
In reference to the additional external substances and the target population, recent studies have published findings concerning the effects of antidepressant use during pregnancy. Cohen and colleagues (2006) compared the risk of depression relapse in pregnant women who discontinued antidepressant medication with women who maintained treatment during pregnancy. The study enrolled 201 pregnant women with a history of major depression prior to pregnancy, all were less than 16 weeks into pregnancy, and were currently or recently receiving antidepressant treatment (Cohen et al., 2006). The study found that women who discontinued antidepressant therapy had more relapses than those who maintained their medication regimens (Cohen et al., 2006). Of those who discontinued use, 68% experienced relapses of depression during pregnancy, while only 26% of those who maintained medication did the same (Cohen et al., 2006). These findings, although somewhat small in their overall effect, demonstrate that even with the continued use of antidepressants women in the perinatal period can still experience depression during this sensitive and significant time in their lives, resulting in unwanted distress to their mental well-being.

**IV) Rationale**

Based on the evidence presented in these aforementioned research studies, an association between environmental toxicants and mental health does appear to exist. However, the association between the environment and postpartum depression has not been widely explored since most risk factors have been predetermined as either being biological or psychosocial.

Therefore, this topic can be seen as being informative for future research given the increasing prevalence of postpartum depression and the lack of consideration for non-physiological risk factors (i.e. environment). We are constantly exposed to a variety of environmental toxicants and substances, often without awareness to the extent of this exposure, with a great potential to profoundly impact our health. With respect to the referenced literature, it is evident that the environment and its vast array of toxicants can affect someone's mental health through exposure, but what still remains uncertain is which toxicants in particular are of greater risk. Once identified, this could contribute to future studies in the eventual evaluation of these toxicants relative to mental health.

## Chapter 2: Methodology



The methodology comprised of a systematic review of the literature which explored and analyzed the research that has already been carried out that demonstrates an apparent association between environmental toxicants and postpartum depression.

**I) Rationale for the Systematic Review**

The link between adverse health effects and exposure to environmental hazards has been well established, however, given this context, there needs to be consideration for how exposure to environmental toxicants may create adverse psychological health effects, specifically their link to postpartum depression. For example, a systematic review conducted by Rossignol, Genuis, and Frye (2014) demonstrated evidence of such a relationship between environmental toxicants and the development of autism spectrum disorder (ASD). They examined ASD risk and gestational exposure to pesticides and found that prenatal exposure was associated with an increased risk of ASD in children of mothers who lived within 500 m of fields that had the highest quartile of estimated pesticide exposure (Rossignol et al., 2014). Thus, an association between environmental toxicants and mental health does exist and has been investigated using the systematic review methodology. However, the association between the environment and postpartum depression has not been widely explored since most risk factors have been predetermined as either being biological or psychosocial.

In keeping with a similar approach to Rossignol and colleagues (2014), conducting a systematic review allows us to determine the extent to which the current research literature has investigated and explored the association between environmental toxicants and the development of postpartum depression. Upon gathering the findings from a variety of studies, it will be possible to establish any apparent gaps in the understanding of this association as well as the current state of the overall comprehension of the harmful effects to maternal mental health when exposed to such toxicants.

A systematic review exploring this association will help us glean some information as to which types of toxicants might be risk factors for this affective mental health condition. This

type of review is systematic because the methods used to survey the literature and then select the articles to be included in the analysis, are explicit and reproducible. In other words, similar results should be obtained if the process is repeated. The review is also comprehensive because it assesses which different combinations of locations, subjects, variables, and responses have been examined by researchers, and what they have found (Pickering & Byrne, 2013). By mapping the literature, it is possible to highlight the boundaries around generalizations derived from the literature and also the limits of those generalizations (Pickering & Byrne, 2013). The review is also structured because the process for collecting and analyzing the literature follows a series of clear steps (Pickering & Byrne, 2013). Furthermore, systematic reviews can include knowledge generated through both qualitative techniques (e.g. interviews, content and text analysis, case studies, observations, etc.), as well as quantitative approaches (e.g. questionnaire surveys, field-studies and samples, field experiments, etc.) (Pickering et al., 2014). For the purposes of this thesis project, both types of techniques will be considered when reviewing the literature. The publications which agree with the predetermined inclusion criteria will be entered into a personal database (Covidence, in collaboration with Cochrane Reviews), where they will be organized into different categories and subcategories. Covidence allows for title and abstract screening, importing citations, uploading references, full-text screening, completing the quality assessments, and extracting the data. The major difference between this method and narrative literature reviews is that it produces knowledge about 'what we know' as well as 'what we do not know' by identifying research trends and gaps (Pickering et al., 2014). This key difference of systematic reviews is important in acknowledging what needs to be considered for future research in order to gain a greater understanding of the subject matter (i.e. how environmental toxicants relate to the development of postpartum depression).

**II) Objectives**

The overarching aim of this thesis consists of conducting a systematic review of the literature in order to assess whether environmental toxicants are related to postpartum depression. It will explore the issue of environmental toxicants as risk factors for developing postpartum depression among women of reproductive age (15-49 years old), single or married, first-time pregnancy or otherwise, and among either low-, middle-, or high-socioeconomic status.

More specific research objectives include:

1. Determine if the literature supports a link between exposure to environmental toxicants and postpartum depression;
2. Assess whether there are specific classes of environmental toxicants that provide a higher risk for postpartum depression.

**III) Research Question**

This systematic review was directed by the following research question: does prenatal and/or perinatal exposure to environmental toxicants present as a risk factor for women in developing postpartum depression?

**IV) Criteria for Considering Studies for this Review**

**a) Types of studies**

The following types of publications were considered for the systematic review: journal articles (peer-reviewed), reviews (literature, intervention, and systematic), prospective studies, longitudinal studies, follow-up studies, cross-sectional (prevalence) studies, research in progress studies, and conference proceedings/abstracts. All publications which comprised of internal studies were considered for this review.

**b) Types of participants**

The participants for this systematic review include women of reproductive age (15-49 years old - as defined by the World Health Organization (2006)), single or married, first-time pregnancy or otherwise, vaginal or Caesarean birth (though in some studies this was not specified), and among either low-, middle-, or high-socioeconomic status. Studies that included men as primary participants, as well as any study investigating environmental effects on paternal mental health were excluded from this review.

**c) Types of interventions**

The studies which investigated prenatal/perinatal exposure to the following environmental toxicants were considered for this review: carbon monoxide, tobacco smoke, molds/biologic pollutants, lead/heavy metals, pesticides/disinfectants, methylmercury, plasticizers (BPA and phthalates), solvents, and asbestos. The following external substances present in the perinatal environment were also considered for this review: antidepressants (sertraline and nortriptyline), dietary supplements (vitamin A, vitamin B, vitamin C, vitamin D, vitamin $B_{12}$, omega-3 fatty acids, calcium, zinc, magnesium, selenium, iron, and folate) and oral contraceptives.

There was also the consideration for caffeine and alcohol to be investigated in relation to the development of postpartum depression, however, these substances were ultimately not included for the purposes of this systematic review. This decision reflected the notion that these types of studies could have potentially skewed the findings in favour of these two substances, given that there exists an abundance of literature pertaining to caffeine intake and alcohol consumption and their association with the development postpartum mood disorders. The focus of this systematic review was to investigate environmental toxicants which are recognized as

being underreported in the literature in relation to the development of postpartum mood disorders, specifically postpartum depression (i.e. pesticides and air pollution).

**d) Types of outcome measures**

The following outcome measure was to determine if the participants developed postpartum depression as well as postpartum depressive symptoms after exposure to environmental toxicants in the prenatal and/or perinatal period. This systematic review did not control for other comorbidities among the participants.

There exists a variety of methods for testing for the onset of postpartum depression and the presence of postpartum depressive symptoms. For the purposes of this review, all types of methods for the potential diagnosis of such symptoms were considered: Edinburgh Postnatal Depression Scale (EPDS), Beck's Depression Inventory II (BDI-II), and the Hamilton Rating Scale for Depression (HAM-D). The EPDS is a set of 10 screening questions with a rating scale of 0-3 for each question. A high score is considered as a total of $14^{+}$ points and warrants a positive screen for postpartum depression. The BDI-II is a set of 21 questions with a rating scale of 0-3 for each question. A range of 31-40 points is assessed as 'severe depression' and a high score of $40^{+}$ points is assessed as 'extreme depression'. The HAM-D is a set of 17 questions with a rating scale of 0-4 for each question. A high score is considered as a total of $20^{+}$ points and indicates the presence of at least moderately severe depression. In addition, this review also considered those studies which used self-developed questions in order to test the participants for postpartum depression and its associating symptoms. Although these studies did not use an official method to determine the onset of postpartum depression, this was considered when assessing the quality of those studies.

**V) Search Methods for Identification of Studies**

**a) Key words**

A general list of key words (i.e. search terms) was developed to correspond with terms related to both fields of interest - environmental toxicology and postpartum depression (mental health). The search terms were developed with the assistance of a Health Science librarian at the University of Ottawa. In addition, subheadings were included in the search criteria (where appropriate) in order to associate the terms which focus on a specific aspect of the research topic.

A certain amount of trial and error was required to identify the best key words for each of the databases, given their different set of backgrounds (for example, PsycINFO focuses more on mental health compared to Toxline, which focuses more on environmental science), therefore certain adjustments were made for the list of key words for each of the databases. The lists of key words for each of the selected the databases are found in Appendix III as this portrays how the search terms were inputted.

**b) Databases searched**

The electronic databases used to systematically search the literature were Medline (Ovid), PsycINFO, EMBASE (Ovid), CINAHL (Ebsco), and Toxline.

**c) Inclusion and exclusion criteria**

The inclusion criteria were defined as: articles published in English, publication years between 1995-2018, and with women of reproductive age (15-49 years old) as study participants. The exclusion criteria were defined as: articles published outside the preferred publication dates, non-English articles, unavailability of full-text articles, as well as any articles not pertinent to the research topic.

**VI) Steps of a Systematic Review**

The straightforward step by step process behind this method dramatically reduced the time, effort, and expertise traditionally required by other methods (Pickering et al., 2014). The steps of a systematic review for this thesis project are highlighted in the flow chart presented as Figure 1 in Appendix I. This current section of the paper explains in detail the required steps necessary for the successful completion of the systematic review.

Step 1 was to identify and carefully define a specific topic within the overall field of research, and as previously addressed, the topic chosen was to investigate whether environmental toxicants are predisposing factors for postpartum depression. It has been found that the systematic review method works well for emerging areas, which seemed appropriate for this project as the relationship between the environment and mental illnesses has been moderately researched.

Next, it was important to identify the types of questions that should be addressed by the literature review, which in turn, helped to establish the research question (Step 2). The following characteristics were assessed and determined for development of the research question as well as the inclusion criteria: articles published in English, publication years between 1995-2018, and with women of reproductive age (15-49 years old) as study participants. It was decided to broaden the study location and consider articles with international samples instead of solely North American studies. A preliminary search revealed that there were very few North American studies in the search results and therefore, was not deemed as a sufficient number to include in the systematic review. The majority of the search results comprised of global studies relating to environmental toxicants and postpartum depression and with the consideration for international studies, this allows for a much greater number of articles to be included in the review. The

exclusion criteria were: articles published outside the preferred publication dates, non-English articles, unavailability of full-text articles, as well as any articles not pertinent to the research topic.

Once the topic and research question were identified, key words were selected (Step 3) and were used to search the electronic databases for relevant articles. The search terms were developed with the assistance of a Health Science librarian at the University of Ottawa. In addition, subheadings were included in the search criteria in order to associate the terms which focus on a specific aspect of the research topic.

The next step (Step 4) was to appropriately select and search the scholarly databases for the systematic review. To reiterate, the electronic databases selected and searched for this systematic review were: Medline (Ovid), PsycINFO, EMBASE (Ovid), CINAHL (Ebsco), and Toxline. Following consultation with the Health Sciences librarian regarding which databases should be used for the systematic review, it was mentioned that GenderWatch would not be best suited for this type of research question (as was originally suggested), since this database focuses primarily on women's studies and not entirely related to health research. CINAHL was then suggested to use in its place, as this database was believed to contain a variety of articles more pertinent to the research topic. Using different databases provides the best results for the review and allows to cross check if the searches are sufficiently comprehensive. The search results for each of the databases were imported onto the Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) (via uploaded RIS file formats). This software allowed for the removal of any duplicates across the five databases and this was also how the article screening processes were conducted, as identified in the next step.

Step 5 involved reading and assessing each publication. This screening process was completed in two stages: 1) screening articles by title/abstract; 2) full-text screening. The inclusion and exclusion criteria were carefully considered during each stage of the screening process and were carefully clarified at this point in the review to ensure that the results would be reproducible. In some cases, reading the title and abstract was sufficient to exclude potential publications, whereas for others, it was necessary to carefully read the entire paper, for being the final justification of its inclusion or exclusion. The screening process was also completed a second time, with an additional reviewer (undergraduate student) going through the list of articles from each of the databases and assessing them with the same inclusion and exclusion criteria. After the second reviewer completed both stages of the screening process, the final number of articles to include in the systematic review were determined and included for data analysis. The use of a second reviewer for the screening process was needed in order to establish reliability with the final results and contributed to the 'systematic' aspect of this review.

After selecting the final number of articles, the next step was to develop the structure of the personal database on the topic presented (Step 6). Each paper was assigned to a single row in the spreadsheet and the categories/subcategories become the columns. Structuring the personal database involved selecting and defining the categories of data which were to be filled with information about each article selected through the electronic searches. Please refer to Table 1 in Appendix II which contains the final number of articles and the associating information as defined by each category (Step 7). As each article was inputted into the personal database, some revisions were made in order to make sure that all the information was inputted correctly into the table and to ensure that no pertinent information was missed (Step 8).

The personal database was then used to produce summary tables which lists the number and/or percentage of articles with varying study designs and the different classes of environmental toxicants investigated among the included studies (Step 9). Again, the categories, subcategories, and criteria were continuously reviewed, and sometimes required the database and summary tables to be updated. Please refer to Table 2 in Appendix II, which represents the summary table highlighting the number of articles in each category.

The process of selecting the articles from the chosen databases is represented in a flow diagram (PRISMA), which identified the stages of narrowing down the number of articles which were included in the systematic review, as well as reasons for excluding certain articles. Please refer to Figure 2 in Appendix I which outlines the identification and assessment of the included studies in this systematic review represented as a PRISMA flow diagram.

Step 10 involved carefully assessing the summary tables of the results which documents the breadth, depth, and type of published literature on the topic. This determined which results were the most important and why, and therefore led to Step 11 which involved data extraction. The types of data extracted from each of the included studies were study characteristics and participant demographics. Study characteristics comprised of: study design; where and when the study was conducted; number of participants; intervention(s) and comparator(s), if appropriate; study outcomes (including which were primary outcomes and which were secondary, and which were pre-specified); analyses; and length of follow-up (if appropriate). Participants' demographic information comprised of documenting participants' age, sex, and ethnicity. Please refer to Table 3 (study characteristics) and Table 4 (participant characteristics) in Appendix II for the complete set of data extraction tables. After finalizing the data extraction tables, the last step entailed analyzing the data and reporting the findings.

**VII) Data Analysis**

A narrative synthesis of the data was chosen as the primary method of data analysis for this review. Since there are only four randomized controlled trials in this systematic review out of the thirty included studies, it appears to be more appropriate to synthesize the data narratively, instead of conducting a meta-analysis. A meta-analysis allows the researcher to determine an overall measure of the intervention effect and given that there are only a small number of randomized studies in this review, it would be implausible to determine the true magnitude of the intervention effect.

A narrative synthesis was used to describe the data from the included studies (randomized controlled trials, non-randomized studies (e.g. cohort and cross-sectional) and various literature reviews). This refers to the presentation of the results using words only with reference to the data tables. Data extraction tables were completed after inputting the study characteristics and participant characteristics from each of the included studies, which were then developed as final data tables to constitute the narrative synthesis.

**VIII) Quality Assessment**

In addition to the article selection process, the Covidence software also examines the quality of each included study. The quality assessment component of the systematic review entailed evaluating whether the studies have been designed, conducted, and reported in such a way that they can be considered reliable (i.e. having rigour) and whether or not they provide meaningful answers to the research question (i.e. have relevance) (Boland, Cherry, & Dickson, 2017). The ‘quality’ of each study refers to: the degree to which a study employs measures to minimize bias and error in its design, conduct, and analysis (Khan et al., 2003). This component is necessary for a systematic review in order to establish confidence that both the study’s design

and conduct are sufficiently robust for the results of the study to be trustworthy and generalizable (Boland et al., 2017).

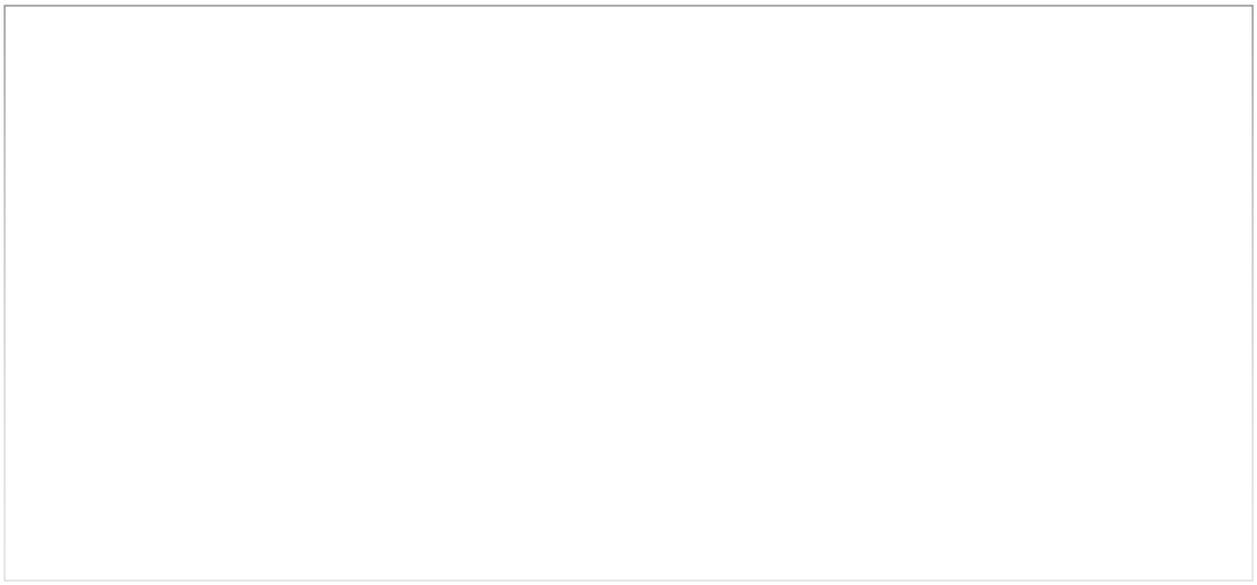
A key element to assessing the quality of the study is to ask questions about bias. This includes evaluating the following biases among the studies: selection (were the individuals selected to participate in the study likely to be representative of the population? How were they selected?), allocation (how were the participants allocated to the treatment groups? Could anyone in the study predict or control the allocation?), performance (were the participants, providers of the intervention or the study investigators aware of the treatment that participants received? Were they blinded?), detection (were the people who measured the study outcomes aware of which treatment participants received or were they blinded?), attrition (what proportion of people in each group stopped having the treatment? Did they stop themselves (dropout) or by study personnel (withdrawal)?), and reporting (were all outcomes stated to be measured actually reported or did the study authors fail to report outcomes that showed no (or negative) effect?) (Boland et al., 2017).

There are different types of quality assessment tools for evaluating each study type. In randomized controlled trials, participants are randomly assigned to intervention groups. In non-randomized studies, participants might be assigned to different groups but not in a random manner, or the study might describe a group (or groups) of participants who are either followed up over a period of time or examined at one specific time point. Between the 30 included studies in this systematic review, there were 4 randomized controlled trials, 11 literature reviews, 10 cohort studies, and 5 cross-sectional studies. As suggested by Boland and colleagues (2017), a design-specific quality assessment was used for each of the different study types. The Cochrane Handbook (Higgins & Green, 2011) recommends using a Risk of Bias tool for assessing the

quality of randomized controlled trials. This involves a judgment and a support for the judgment for each entry in a 'Risk of Bias' table, where each entry addresses a specific aspect of the study. The judgment for each entry comprises of assessing the risk of bias as 'low risk', 'high risk', or 'unclear risk', with the last category indicating either lack of information or uncertainty over the potential for bias. All judgments in this tool must be supported by a brief summary of the evidence underlying the judgment. Please refer to Appendix II for the complete Risk of Bias tables for the four randomized controlled trials included in the systematic review.

For non-randomized studies, different quality assessment tools/checklists were used to assess the literature reviews and the cohort study designs. The Critical Appraisal Skills Programme (CASP) contains quality assessment checklists for both cohort studies and literature reviews. This tool enables researchers to systematically assess the trustworthiness, relevance and results of published papers ("Home - CASP", 2018). Lastly, the Downs and Black (1998) 27-item checklist was used to assess the quality of the cross-sectional studies. Among the selected resources for quality assessment tools suggested by Boland and colleagues (2017), there were no tools specializing in cross-sectional studies. The Downs and Black (1998) checklist can be used for non-randomized studies and has been considered suitable for use in systematic reviews that include these types of studies. This tool can be used to assess the quality of original or primary source research articles and to synthesize evidence from quantitative studies ("Quality checklist for health care intervention studies", n.d.). It was easy to use and provided both an overall score for study quality and a numeric score out of a possible 30 points, including questions about: study quality, external validity, study bias, confounding and selection bias, and power of study ("Quality checklist…", n.d.).

# Chapter 3: Results



**I) Search Results**

**a) Selection criteria**

The search results from each of the databases were imported into the Covidence software; this allowed for the identification and subsequent removal of any duplicates across the five databases. Please refer to Figure 2 in Appendix I outlining the identification and assessment of the included studies in this systematic review represented as a PRISMA flow diagram.

A total of 835 studies were imported from screening. A total of 270 duplicates were removed. From there, 565 studies were screened based on the title and abstract as well as the predetermined inclusion criteria (articles published in English, publication years between 1995-2018, and with women of reproductive age (15-49 years old) as study participants). Reasons for exclusion: articles published outside the preferred publication dates, non-English articles, unavailability of full-text articles, in addition to any articles not pertinent to the research topic.

Of these, 500 studies were deemed irrelevant and were therefore excluded from the review. Therefore, 65 studies were screened based on the full-text, while 35 were excluded as these studies did not have full-text available (n=9), resulted in different study outcomes (other mental health conditions such as anxiety and suicidality) (n=9), comprised of the wrong interventions (e.g. non-environmental toxicants) (n=8), were unrelated to the research question (n=4), incorrect study design (n=2), duplicate (n=1), not published in English (n=1), and contained the wrong study population (e.g. men, children) (n=1). A final number of 30 studies were included for the systematic review.

**b) Personal database**

The personal database is comprised of the 30 included studies for the systematic review (each article was assigned to a single row) along with the individual study characteristics (columns). This database was then used to produce summary tables of the study designs and classes of environmental toxicants identified amongst the included studies, which will be presented in a subsequent section (III).

Please refer to Table 1 in Appendix II containing the final number of articles and the associating characteristics as defined by each category.

**II) Included Studies**

**a) Study designs**

The 30 articles included in this review comprised of a variety of study designs. The types of study designs across all 30 articles were as follows: 11 literature reviews (including systematic and intervention) (37%), 10 cohort studies (33%), 5 cross-sectional studies (17%), and 4 randomized controlled trials (13%). Table 2 in Appendix II showcases the summary of the

number of articles in each category. The inclusion of secondary data contributes to the overall investigation of this topic by exploring the comprehensive findings from prior literature reviews in order to obtain a greater sense of the extent to which these environmental toxicants have been previously reported in the literature in relation to postpartum depression. However, it is important to note that this ultimately lessens the rigour of this systematic review, as it affects the validity and reliability of the systematic review by including both primary and secondary data in the analysis and by impacting the exact replicability of the findings which were generated from the methodological process.

**b) Classes of environmental toxicants**

There were six categories of environmental toxicants which were studied among the 30 included articles in this systematic review. The categories and the associated number of articles (n) for each are:

1. Cigarette smoke exposure (n=14)
    - Active smoking and second-hand smoke
2. Dietary supplements (n=8)
    - Micronutrients, vitamins, omega-3 fatty acids
3. Antidepressants (n=5)
    - Sertraline and nortriptyline
4. Air pollution (n=1)
    - Particulate air pollution
5. Oral contraceptives (n=1)
    - Depot medroxyprogesterone acetate (DMPA)
6. Pesticides (n=1)
    - Organochlorine pesticides

Please refer to Table 2 in Appendix II as the summary table representing the number of articles for each class of toxicants.

**III) Data Extraction**

Based on the findings from the included studies, prenatal/perinatal exposure to active/passive smoke was largely found to increase the risk of developing postpartum depression and depressive symptoms in the postpartum period. Prenatal active smoking was found to be associated with and increased risk for postpartum depression, particularly those who smoked prior to pregnancy and continued to smoke during pregnancy into the postpartum period, compared to those women who quit during pregnancy and those who were non-smokers (Chen et al., 2018; Dagher & Shenassa, 2012; Frandsen, Thow, & Ferguson, 2017; Munafò, Heron, & Araya, 2008; Salimi et al., 2015; Vivilaki et al., 2016). The study by Underwood et al. (2017) did not find an association between prenatal active smoking and postpartum depression. Perhaps the reason this study did not find an association between prenatal active smoking and postpartum depression could be because these investigators also measured perceived stress and alcohol consumption along with smoking status. The perceived stress experienced by the participants was significantly associated with the development of postpartum depressive symptoms and surpassed the presence of an association between prenatal active smoking and postpartum depression. The other studies which investigated active smoking exposure did not include any other factors in their outcome measurement and only focused on prenatal smoking. This in turn, could explain the difference in findings between these studies.

The studies which investigated dietary supplements found mixed results overall, however, omega-3 fatty acid intake was found to be the most beneficial in reducing depressive symptoms in the postpartum period. These studies which focused on omega-3 fatty acids were

able to demonstrate a reduced risk of depression in the postpartum period with prenatal and/or perinatal consumption (Coletta, Bell, & Roman, 2010; Glenville, 2006; Leung & Kaplan, 2009) and identifying a decrease in EPDS scores by 52% (Freeman, 2006). However, there were other studies with opposite results pertaining to omega-3 fatty acids, in that omega-3 fatty acid intake and postpartum depression incidence findings are contradictory and with varying results (Derbyshire & Costarelli, 2008; Ellsworth-Bowers & Corwin, 2012). These variations could be reflected on their literature review study design. As noted by Derbyshire and Costarelli (2008), the lack of associations may be a result of low supplement dosages, under-reporting of fatty acid intake, short-term follow-up, and unsuitable ratios of EPA:DHA among the included studies. Furthermore, these investigators are primarily reporting preliminary findings in their reviews and that more larger studies and randomized controlled trials are recommended in order to further investigate this association.

The studies which investigated antidepressants found that sertraline was more likely to exhibit preventative effects in developing postpartum depression and reduce the extent of depressive symptoms in the postpartum period. These studies found that sertraline was more effective in reducing the risk of developing postpartum depression and experiencing postpartum depressive symptoms compared to nortriptyline (Howard et al., 2005; Molyneaux et al., 2018; Pariser, Nasrallah, & Gardner, 1997). Other studies compared sertraline with a placebo in treating postpartum depression. Hantsoo et al. (2014) found that sertraline produced a significantly greater response rate (59%) than placebo (26%) and more than a two-fold increased remission rate. Sunder et al. (2004) compared sertraline to a placebo and postpartum depression and they found no significant difference between the two in preventing postpartum depression. Both studies by Hantsoo et al. (2014) and Sunder et al. (2004) were randomized controlled trials

and they each had relatively small number of participants (38 and 11 women respectively). Considering the small number of participants for these two studies, this presents as a possible limitation in that there were not equal distributions between the intervention groups and could have therefore had an influence on the overall results.

The one study that investigated air pollution found that increased particulate air pollution exposure was associated with an increased risk in depressive symptoms in the postpartum period. Sheffield et al. (2018) aimed to determine a link between air pollution exposure with psychological functioning among postpartum women. The participants included an ethnically diverse, lower income urban cohort of pregnant women. The results demonstrated an association between prenatal ambient $PM_{2.5}$ exposure levels and postpartum total EPDS and the investigators observed a statistically significant sensitive window of $PM_{2.5}$ exposure for elevated anhedonia subscale scores during mid-pregnancy, especially gestational weeks 13 to 20 (Sheffield et al., 2018). In stratified analyses, effects were most evident among African-American women. For this group of women, increased exposure to $PM_{2.5}$ was significantly associated with higher total postpartum EPDS scores as well as higher scores on the depressive and anhedonia symptom subscales, with minor variability in the identified window of vulnerability in pregnancy across these outcome measures (Sheffield et al., 2018).

The one study that investigated oral contraceptive use in the perinatal period found an association with an increased risk of depressive symptoms in the postpartum period. Singata-Madiliki, Hofmeyr, and Lawrie (2016) aimed to determine whether DMPA (the most commonly used postnatal contraception option in South Africa) increases the risk of postpartum depression compared with the intrauterine device (IUD) when administered after delivery (within 48 hours of childbirth). The finding from this study indicated that one-month depression scores were

significantly higher with DMPA use compared with IUD use according to EPDS data; 3-month depression scores were higher with DMPA according to the BDI-II data. Although the results are highly suggestive of a higher risk of postpartum depression with DMPA, the trial findings cannot be regarded as conclusive (Singata-Madiliki et al., 2016).

Lastly, the one study that investigated pesticide exposure found no associative risk in developing postpartum depression. Yalçin et al. (2015) aimed to determine the levels of organochlorine pesticides (OCPs) in breast milk and to evaluate the relation between OCPs and maternal psychopathologies. The authors state that breast milk is a unique biological matrix for investigating certain environmental contaminants because it can provide exposure information about the mother and her breastfed infant (Thundiyil, Solomon, & Miller, 2007). The results of this study identified and analyzed 12 OCPs among the 75 samples and found that no relation was detected between EPDS and OCPs (Yalçin et al., 2015).

The participants among the included studies were female and of an average age between 28-35 years old. This age range represents the notion that the potential for exposure to certain toxicants lessens for women of younger age. Furthermore, the participants were of various ethnicities: Caucasian, African-American, Hispanic, Asian, Native American, or unlisted.

Please refer to Table 3 (study characteristics) and Table 4 (participant characteristics) in Appendix II for the complete set of data extraction tables. The production of these tables by means of a narrative synthesis enables the examination of the similarities and differences between the included studies and warrants descriptive conclusions based on the present summary of the current knowledge surrounding this research topic.

**IV) Quality Score Assessment**

**a) Literature reviews**

The quality of the literature reviews (including systematic and intervention) (n=11) was assessed using the CASP (The Critical Appraisal Skills Programme) checklist. This tool enables researchers to systematically assess the trustworthiness, relevance and results of published papers ("Home - CASP", 2018). These checklists were designed to be used as educational teaching tools, as part of a workshop setting and do not suggest a scoring system ("CASP Systematic Review", 2018). The core CASP checklists (randomized controlled trial and systematic review) were based on JAMA 'Users' guides to the medical literature adapted from Guyatt, Sackett, and Cook (1994), and piloted with health care practitioners ("CASP – Systematic Review", 2018). These checklists target three main categories for assessing the quality of each study: are the results of the study valid? What are the results? And will the results help locally? The CASP checklist for cohort studies contain 12 questions and the checklist for literature reviews contain 10 questions. The answers to the questions can either be yes/can't tell/no and with the option to add any notable comments in order to support the answer given.

**b) Cohort studies**

The quality of the cohort studies (n=10) was assessed using the CASP (The Critical Appraisal Skills Programme) checklist.

**c) Cross-sectional studies**

The quality of the cross-sectional studies (n=5) was assessed using the Downs and Black checklist. Among the selected resources for quality assessment tools suggested by Boland and colleagues (2017), there were no tools specializing in cross-sectional studies. The Downs and

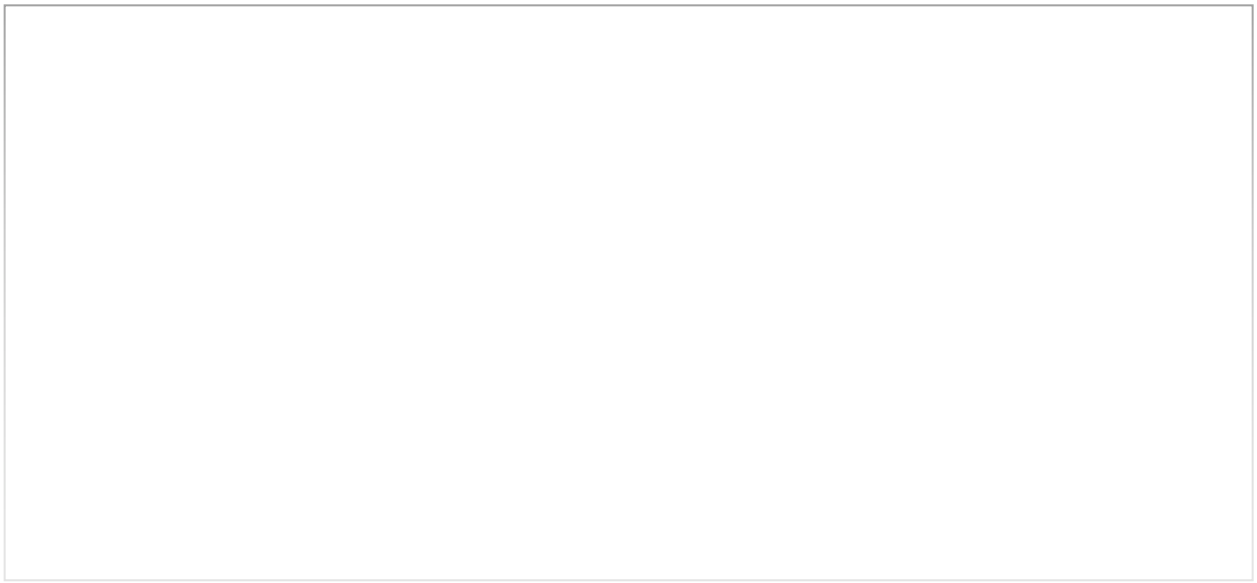
Black (1998) checklist can be used for non-randomized studies and has been considered suitable for use in systematic reviews that include these types of studies. This quality assessment tool is a 27-item checklist with the options of answering yes/no/unable to determine for each question. There are 10 questions related to overall study quality, 3 questions relating to external validity (representativeness of the findings of the study and whether they can be generalized to the population where the participants were derived), 13 questions relating to internal validity (biases), and 1 question relating to study power (to determine if the negative findings from the study are due to chance). This checklist provides an overall score for study quality as well as a numeric score out of a possible 31 points.

**d) Randomized-controlled trials**

The quality of the randomized controlled trials (n=4) was assessed using the Cochrane Risk of Bias Tool. The Fard et al. (2017) study was judged as 'low risk' of bias, therefore of good quality. The Hantsoo et al. (2014) study had an overall judgment of 'low risk' of bias with two domains judged as 'high risk', therefore of adequate quality. The Singata-Madiliki et al. (2016) study was judged as 'low risk' of bias, therefore of good quality. Lastly, the Sunder et al. (2004) study had an overall judgment of 'high risk' of bias, therefore of poor quality.

Please refer to Tables 5-8 in Appendix II for the complete set of Risk of Bias tables for the randomized controlled trials.

# Chapter 4: Discussion



### I) Main Findings

The objectives for this systematic review were to determine if the literature supports a link between exposure to environmental toxicants (xenobiotics) and postpartum depression and to assess whether there are specific classes of these that may provide a higher risk for postpartum depression. The main findings indicate that prenatal/perinatal women exposed to active/passive smoke (cigarette/tobacco) had the greatest risk in developing postpartum depression and depressive symptoms in the postpartum period, compared to the other categories of toxicants. The literature does support a link between certain environmental toxicants and postpartum depression (Chen et al., 2018; Dagher & Shenassa, 2012; Frandsen et al., 2017; Munafò et al., 2008; Salimi et al., 2015; Vivilaki et al., 2016; Sheffield et al., 2018; Singata-Madiliki et al., 2016), although there were studies with inconclusive results and/or that found no association. These observations will be further explained throughout the following sections and the results for

each category of toxicant will be interpreted. Please refer to Table 1 in Appendix II highlighting each of the investigated toxicants from the included studies and the resulting outcomes.

An important finding from this review is represented among the studies which focus on cigarette/tobacco smoke exposure. These studies reported that exposure to this toxicant during the prenatal and/or perinatal period was primarily found to increase the risk of developing postpartum depression and depressive symptoms in the postpartum period. It is already well known that active smoking can have harmful effects to one's health by increasing the risk of lung cancer and respiratory conditions (Papadopoulos et al., 2011; Sousa et al., 2019; Laniado-Laborín, 2009; Hawari et al., 2019), however the studies in this review demonstrated that not only does tobacco exposure affect physical health but can most notably affect mental health. The prenatal and perinatal periods are sensitive times for women as they are undergoing physiological changes (Soma-Pillay et al., 2016; Talbot & Maclennan, 2016) and experiencing drastic lifestyle changes (relating to sleep, diet, exercise, etc.) (Hall et al., 2009; Chien & Ko, 2004; Barakat et al., 2015; Danielewicz et al., 2017), and with the introduction of harmful toxic chemicals to their bodies, this has been shown to ultimately affect their mental health well into the postpartum period, resulting in the experience of major depressive symptoms (see Table 1 in Appendix II). The importance of recognizing the harmful effects of tobacco exposure during the prenatal and perinatal periods will further advance research in the investigation of this association and will hopefully create awareness of relating tobacco exposure to mental health.

Given the major presence of cigarette/tobacco smoke studies, we acknowledge the limited amount of evidence regarding the other toxicants identified in this review and their relationship with postpartum depression; investigation of the relationship between mental health and air

pollution or pesticide exposure is particularly lacking. More often than not, people are unaware and inattentive to what they are regularly exposed to in the environment especially regarding those toxicants, for which it is difficult to measure their underlying effects on physical health (i.e. difficult to determine the amount of levels of these toxicants as they can be airborne). However, in a study included in this review, investigators did find the means to measure exposure levels and thus, were able to associate them with postpartum depression among their participants. From these experimental tools, we see a potential for measuring other pollutants present in the maternal environment in order to target their relationship with other mental health disorders in the same way. Aside from cigarette/tobacco smoke, more research is necessary for investigation of other categories of toxicants and their effects on maternal health, in order to gather a greater understanding of the most advantageous techniques in addressing this association.

**II) Categories of Toxicants**

**a) Cigarette (tobacco) exposure (active and passive)**

Among the included studies, there were 14 which investigated active and/or passive smoke exposure and postpartum depression. The overall findings from these studies were that prenatal/perinatal smoke exposure was largely found to increase the risk of developing postpartum depression and/or experience postpartum depressive symptoms.

Prenatal active smoking was found to be associated with an increased risk for postpartum depression, particularly those who smoked prior to pregnancy and continued to smoke during pregnancy into the postpartum period, compared to those women who quit during pregnancy and those who were non-smokers (Chen et al., 2018; Dagher & Shenassa, 2012; Frandsen et al.,

2017; Munafò et al., 2008; Salimi et al., 2015; Vivilaki et al., 2016). The study by Underwood et al. (2017) did not find an association between prenatal active smoking and postpartum depression. This study was conducted in New Zealand as a longitudinal cohort of 5,301 women. The objective was to explore whether risk factors differ for depression symptoms that are present during pregnancy and/or after childbirth. The defined antenatal depressive symptoms (ADS) as the time throughout pregnancy and postpartum depression symptoms (PDS) as a year after childbirth. The antenatal data were collected during face-to-face interviews during the third trimester and the postpartum data were collected 9 months after childbirth using the same method. Both ADS and PDS were measured using the EPDS. Self-reported health data were collected during the antenatal interview where the participants reported their smoking behaviour and alcohol consumption before and during pregnancy. The findings demonstrated that only a small group of women (3% of the total sample) experienced depression symptoms 9 months after childbirth. The factors significantly associated with PDS at 9 months after childbirth were 1) perceived stress scores and 2) not being employed in a paid job during pregnancy (Underwood et al., 2017). Perhaps the reason this study did not find an association between prenatal active smoking and postpartum depression could be because these investigators also measured perceived stress and alcohol consumption along with smoking status. The perceived stress experienced by the participants was significantly associated with the development of postpartum depressive symptoms and surpassed the presence of an association between prenatal active smoking and postpartum depression. The other studies which investigated active smoking exposure did not include any other factors in their outcome measurement and only focused on prenatal smoking. This in turn, could explain the difference in findings between these studies.

Second-hand smoke (SHS) exposure during the prenatal and/or perinatal was found to be associated with an elevated risk for postpartum depression (Alibekova et al., 2016; Mbah et al., 2013; Song et al., 2018, Weng et al., 2016). Additionally, Khan et al. (2015) found that SHS exposure in the prenatal period was associated with almost twice the odds of postpartum depressive symptoms. The study by Kalayasiri, Supcharoen, and Ouiyanukoon (2018) did not find an association between prenatal passive smoking and postpartum depression. This cross-sectional study was conducted in Thailand with 106 postpartum women as participants (6-weeks after childbirth). The investigators used the EPDS to measure for postpartum depression and the data on SHS were obtained by verbal report of exposure at the workplace, home, or public spaces using yes/no questions. The findings demonstrated that SHS was not associated with postpartum depression in their cohort, regardless of the high rates of SHS exposure reported by the participants. Perhaps the reason why these findings differ from those of the previous studies, is because of the small number of participants (106 women) and the prevalence of SHS during pregnancy may be underreported because of recall bias of exposure to SHS that may have influenced the overall outcomes (Kalayasiri et al., 2018). In addition, the cross-sectional design of the study could have affected the results as the investigators only measured the smoke exposure at one time point, instead of following these participants for a longer period of time as exhibited in longitudinal studies. These reasons could explain the difference in findings between the studies exploring second-hand smoke exposure.

There was one study in particular which investigated the association between third-hand smoke (THS) exposure during pregnancy and postpartum depression. Wang et al. (2018) state that THS has been the recent discussion of another form of tobacco exposure – defined as residual tobacco smoke contaminants and by-products on materials such as clothing after

extinguishing a tobacco product. THS can remain on indoor walls, fabrics, and other typical household items such as curtains, carpets, sofa upholstery, beds, and chairs for more than 1.5 years (Bahl et al., 2014). The investigators used the EPDS to assess postpartum depression in their study and they measured THS exposure by administering a questionnaire to the participants. For the exposure levels at home, they asked, "during your most recent pregnancy, how many days did you smell cigarette smoke at home when nobody was smoking at home, but someone might have smoked earlier?" and for THS exposure outside the home, they asked the questions "during your recent pregnancy, how many days did you smell cigarette smoke outside your home such as in an office room or in other places when nobody was smoking, but someone might have smoked earlier?" (Wang et al., 2018). The response options for each exposure were categorized into '0 day/week', '1–4 days/week', and '5–7 days/week'. Women who replied 'none' or '0 day/week' to this question were considered as 'unexposed' and women who replied '1–4 days/week' or '5–7 days/week' were considered as 'exposed' to THS during pregnancy (Wang et al., 2018). The findings of this study were that of the 973 puerperal women, 17.8% had postpartum depression and the prevalence of THS exposure during pregnancy was 74.5% (Wang et al., 2018). Compared to those who were never exposed to THS during pregnancy, women who were exposed to a THS environment during pregnancy were at a higher risk of postpartum depression – nearly a two-fold increased risk (Wang et al., 2018). Although this study was conducted in China, it would be interesting to investigate this association furthermore with a North American population as this is among the very few studies present in the current literature which explore the notion of THS and maternal mental health. These findings enhance the understanding of risk factors for postpartum depression and emphasizes the apparent need to address the risk of postpartum depression worldwide.

**b) Antidepressants**

Among the included studies, there were 5 which investigated the intake of antidepressants and postpartum depression. The overall findings from these studies were that antidepressant use during pregnancy was found to demonstrate preventative effects in that they limited the risk of developing postpartum depression.

There were studies which compared different antidepressant drugs to assess their effectiveness in reducing the likelihood of developing postpartum depression, which included the antidepressants sertraline and nortriptyline. These studies found that sertraline was more effective than nortriptyline in reducing the risk of developing postpartum depression and experiencing postpartum depressive symptoms (Howard et al., 2005; Molyneaux et al., 2018; Pariser et al., 1997). Other studies compared sertraline with a placebo in treating postpartum depression. Hantsoo et al. (2014) found that sertraline produced a significantly greater response rate (59%) than placebo (26%) and more than a two-fold increased remission rate (53% vs. 21%). A limitation to this study however, is that there were only 38 postpartum women as participants, which is a relatively small number of participants for a randomized controlled trial. Sunder et al. (2004) conducted another randomized controlled trial which compared the effects of sertraline to a placebo on postpartum depression and they found no significant difference between the two in the prevention of postpartum depression; thus, no effect of sertraline. Similarly, this study had a very small number of participants (11 women) for a randomized controlled trial – 8 women took sertraline and 3 women took the placebo. This small and uneven number of participants in each group could present as a limitation for this study and this could have ultimately affected the findings in that there were not enough women taking the placebo compared to sertraline, which could have had an influence on the results.

Upon searching the database for relevant articles to include in the systematic review relating to antidepressants, there were a large number of studies exploring the potentially negative, long-term effects of prenatal antidepressant intake on the child. These studies focused on the long-term neurodevelopmental and motor developmental effects of the child after being exposed prenatally to antidepressants (Hermansen & Melinder, 2015; Galbally, Lewis, & Buist, 2011; Gentile & Galbally, 2011; Grove, Lewis, & Galbally, 2018). An overall appraisal of these findings indicate that children exposed to antidepressants *in utero* score lower on motor subscales and demonstrate some cognitive difficulties and behavioural problems (measured at approximately 2 years of age). These types of studies came up quite frequently when searching the databases for prenatal antidepressant use and it was evident that there were much fewer studies targeting prenatal/perinatal antidepressant use and postpartum mental health. Given the existing growing body of research relating to prenatal antidepressant exposure and the resulting effects on the child, this should not hinder the benefits of using antidepressants in the prenatal/perinatal period as this could contribute to a promising direction in determining how to help and provide treatment to these women who have been greatly affected by this mental health condition.

**c) Dietary supplements**

Among the included studies, there were 8 which investigated the intake of dietary supplements and postpartum depression. There were mixed results from these studies regarding reduced risk of developing postpartum depression and postpartum depressive symptoms, depending on which supplements were investigated.

The studies looked at a variety of dietary and nutritional supplements and their relationship with postpartum depression, which included: omega-3 fatty acids, folate, vitamins (B, D, and

$B^{12}$), calcium, zin, magnesium, selenium, and iron. There were studies which primarily focused on omega-3 fatty acid intake and postpartum depression, and they were able to demonstrate a reduced risk of depression in the postpartum period with their prenatal and/or perinatal consumption (Coletta et al., 2010; Glenville, 2006; Leung & Kaplan, 2009). Additionally, one literature review which identified a 52% reduction in EPDS scores from their included studies (Freeman, 2006). However, there were other studies with contradictory results pertaining to omega-3 fatty acid intake and postpartum depression (Derbyshire & Costarelli, 2008; Ellsworth-Bowers & Corwin, 2012). The studies which focused on other nutritional supplements (e.g. vitamins, calcium, magnesium, etc.) demonstrated varying results as well, in that riboflavin, zinc, and calcium might have played a role in alleviating symptoms of postpartum depression (Derbyshire & Costarelli, 2008) and that there was no significant difference found between zinc and magnesium in reducing postpartum depressive symptoms (Fard et al., 2017). Furthermore, Leung and Kaplan (2009) state that low intake of these nutrients was associated with an increased risk of postpartum depression; however, in the Sparling et al. (2017) review, they state that there is limited evidence regarding the influence of dietary supplement intake on the risk of perinatal depression.

The vast discrepancies among the studies investigating dietary and nutritional supplements and postpartum depression should be noted and demonstrates the need for further studies in this area of research; there exist populations with wide variations in their nutritional intake and the use of these supplements could be beneficial to those affected by postpartum depression. These studies only glean on the importance of targeting these dietary patterns in order to better explain the relationship with postpartum depression (Sparling et al., 2017).

**d) Oral contraceptives**

Among the included studies, there was one which investigated oral contraceptive use (specifically, DMPA) and postpartum depression. The finding from this study was that one-month EPDS depression scores were statistically higher in the DMPA group compared with the copper-containing IUD group.

Singata-Madiliki et al. (2016) conducted a randomized controlled trial in South Africa with 242 postpartum women as the participants. They aimed to determine whether DMPA (the most commonly used postnatal contraception option in South Africa) increases the risk of postpartum depression compared with the IUD when administered after delivery (within 48 hours of childbirth). There were 116 women in the DMPA group and 118 women in the IUD group, distributed by random allocation. Postpartum depression was measured using two study instruments: the EPDS and the Beck Depression Inventory (II) (BDI-II). The BDI-II had been previously validated and used in the same cultural context and translated into the local language (similarly with the EPDS). The finding from this study indicate that one-month depression scores were significantly higher with DMPA use compared with IUD use according to EPDS data; 3-month depression scores were higher with DMPA according to the BDI-II data. Although the results are highly suggestive of a higher risk of postpartum depression with DMPA, the trial findings cannot be regarded as conclusive (Singata-Madiliki et al., 2016). Findings at 3-months were statistically significant for BDI-II measurements only, not for 3-month EPDS measurements, which may be due to the different focus of the instruments, with the EPDS primarily being a screening tool adapted to the postnatal period, whereas the BDI-II includes more somatic questions (e.g. low libido).

Although Singata-Madiliki et al. (2016) did find an interesting association between DMPA use and postpartum depression symptoms, there is an apparent limitation of this study that the

investigators do not mention. This is reflected in their methodology, in that they did not have a control group (i.e. placebo) for either the DMPA intervention or the IUD intervention. Perhaps the investigators of this study did not view this group to be necessary in their research; however, this lack of control group could ultimately contribute to a potential for bias in the overall findings. Since the investigators did not consider confounding factors such as other risk factors for postpartum depression (as mentioned in their limitation section of the article), it would have been beneficial for them to use a control group when comparing the two interventions because of its role in providing a baseline for further comparison of the results in order to validate if the intervention (DMPA or IUD) was responsible for the outcome (postpartum depression).

**e) Air pollution**

Among the included studies, there was one which investigated particulate air pollution exposure and postpartum depression. The finding from this study was that prenatal exposure to particulate matter with diameter ≤ 2.5 μm ($PM_{2.5}$) was significantly associated with higher total postpartum EPDS scores (race-stratified analysis).

Sheffield et al. (2018) conducted a prospective cohort study in the Unites States with 598 postpartum women as participants. They aimed to determine whether there exists a link between air pollution exposure and maternal depressive psychological functioning in the first year postpartum. The investigators included an ethnically diverse, lower income urban cohort of pregnant women to examine this association. The reason for this specific group of participants is demonstrated in the understanding that prevalence rates of anxiety, depressed mood, and anhedonia, are elevated in urban ethnic communities, particularly among African-American and Hispanic mothers and among women of low-socioeconomic status (Liu & Tronick, 2014). Furthermore, the authors highlight the fact that other data suggest that subjective experience of

affective states varies by culture and race/ethnicity (Kanazawa, White, & Hampson, 2007). Taken together, this emphasizes the need to distinguish specific symptom profiles in order to more comprehensively asses risk, particularly among racially/ethnically diverse postpartum women (Sheffield et al., 2018).

The women's daily exposure to $PM_{2.5}$ over gestation was estimated based on their residence during pregnancy. This calculation was done using a validated satellite-based spatio-temporal model that predicts daily ambient concentrations of $PM_{2.5}$. This model uses a mixed model approach by regressing daily surface $PM_{2.5}$ measurements, taken from the U.S. Environmental Protection Agency Air Quality System (AQS) and Interagency Monitoring of Protected Visual Environmental Network, with daily aerosol optical depth measurements, land-use terms, and meteorological variables (Sheffield et al., 2018). This $PM_{2.5}$ model was trained with monitoring data collected by AQS and then validated with 10-fold cross-validation and used to predict daily $PM_{2.5}$ at 1 km x 1 km resolution allowing for the estimations of $PM_{2.5}$ to be calculated for each woman's residential address during her pregnancy (Sheffield et al., 2018). Postpartum psychological functioning was measured using the EPDS at 6 and 12 months postpartum in a face-to-face interview. A number of studies indicate that the EPDS captures multiple domains with the possible variation by race/ethnic subgroups (Hartley et al., 2014; Chiu et al., 2017). The investigators also considered variables that would co-vary with ambient air pollution exposure, including prenatal smoking. Prenatal smoking status was determined by women's self-report at enrollment and in the third trimester and was classified as positive if a woman reported smoking at either visit. Subscale scores in separate models using distributed lag models adjusted for race, education, age, and prenatal smoking

The results demonstrated an association between prenatal ambient $PM_{2.5}$ exposure levels and postpartum total EPDS; the investigators observed a statistically significant sensitive window of $PM_{2.5}$ exposure for elevated anhedonia subscale scores during mid-pregnancy, especially gestational weeks 13 to 20 (Sheffield et al., 2018). In stratified analyses, effects were most evident among African-American women. For this group of women, increased exposure to $PM_{2.5}$ was significantly associated with higher total postpartum EPDS scores as well as higher scores on the depressive and anhedonia symptom subscales with minor variability in the identified window of vulnerability in pregnancy across these outcome measures (Sheffield et al., 2018). As highlighted by the authors, this association is consistent with the emerging understanding of the role of inflammation in mediating anhedonia behaviours via impacts on neurotransmitter synthesis and accumulation of neurotoxic compounds (Pan et al., 2017). It is interesting to note the higher risk for postpartum depression with air pollution exposure among African-American women in this cohort. Although the investigators did demonstrate selection bias in recruiting their study population, they were able to find an association between this exposure and developing postpartum depression and consider this underrepresented population in their study. While this study adds to the growing literature linking ambient air pollution with mental health outcomes in adults, more studies are needed in order to replicate these findings in other populations, particularly with respect to potential windows of vulnerability for the mother during pregnancy, and to further explain the underlying mechanisms (Sheffield et al., 2018).

**f) Pesticides**

Among the included studies, one of which investigated organochlorine pesticide (OCP) exposure and maternal psychopathologies. The finding from this study was that no relation was detected between OCPs and EPDS at 8-months postpartum.

Yalçin et al. (2015) conducted a cross-sectional study in Ankara, Turkey with 72 postpartum women. They aimed to determine the levels of OCPs in the breast milk and to evaluate the relation between these levels and maternal psychopathologies. The authors state that breast milk is a unique biological matrix for investigating certain environmental contaminants because it can provide exposure information about the mother and her breastfed infant (Thundiyil et al., 2007). Furthermore, breastmilk offers a convenient sampling specimen for monitoring the residues of OCPs in human tissues through a non-invasive method (Yalçin et al., 2015). All women fed the baby first and then sample milk aliquots by manual expression into a glass container – avoiding the use of mechanical breast pumps – the aliquots were then frozen consecutively in a glass bottle and stored for future chemical analysis (Yalçin et al., 2015). Postpartum depression was assessed using the EPDS tool at 8-months postpartum. The results of this study identified and analyzed 12 OCPs among the 75 samples. DDTs, B-HCH, aldrin, and heptachlor were detected in, respectively, 89.3, 70.7, 58.7, and 34.7% of the samples and that no relation was detected between EPDS and OCPs (Yalçin et al., 2015). Previously, it had been suggested that high exposure to pesticides, including poisoning, might result in an elevated risk of psychiatric disorders and suicidal behaviour (Ismail, Bodner, & Rohlman, 2012; Freire & Koifman, 2013). However, this study did not find an association between OCP exposure and postpartum depression and as recognized by the investigators, it was the first report assessing the interaction between the levels of OCPs and maternal psychopathologies. A limitation of this study is that the population was primarily from suburban areas with no known exposure, which in turn might limit the generalizability of the results (Yalçin et al., 2015). Future research should investigate other populations and aim to expand this area of research into North American populations for example, to test for pesticide exposure levels (including those related to food and

other agriculture) in order to gain a greater understanding of its vast contamination effect and the possible association with mental health disorders.

**III) Quality Assessment**

Please refer to Tables 5-8 in Appendix II for the Cochrane Risk of Bias assessments for the randomized controlled trials. Please refer to Table 9 in Appendix II as the summary table highlighting the overall quality assessment for each of the non-randomized studies included in the review.

**a) Randomized controlled trials**

The quality of the four randomized controlled trials included in this systematic review were assessed by the Cochrane Risk of Bias tool. This involved a judgment and a support for the judgment for each entry in a 'Risk of Bias' table, where each entry addresses a specific aspect of the study. The judgment for each entry comprised of assessing the risk of bias as 'low risk', 'high risk', or 'unclear risk', with the last category indicating either lack of information or uncertainty over the potential for bias. The following biases were assessed amongst the included studies: selection (were the individuals selected to participate in the study likely to be representative of the population?), allocation (how were the participants allocated to the treatment groups? Could anyone in the study predict or control the allocation?), performance (were the participants, providers of the intervention or the study investigators blinded to the treatment that participants received?), detection (were the people who measured the study outcomes blinded to which treatment participants received?), attrition (what proportion of people in each group stopped having the treatment? Did they stop themselves (dropout) or by study personnel (withdrawal)?), and reporting (were all outcomes stated to be measured actually

reported or did the study authors fail to report outcomes that showed no (or negative) effect?) (Boland et al., 2017).

The Fard et al. (2017) study and the Singata-Madiliki et al. (2016) were the two studies considered to be of 'good' quality, while the Hantsoo et al. (2014) study was considered to be of 'adequate' quality and the Sunder et al. (2004) study to be of 'poor' quality. The risk of bias assessments for each of the four randomized controlled trials are presented as follows.

Firstly, the Fard et al. (2017) study investigated the effects of zinc and magnesium supplements on postpartum depression had an overall 'low' assessment for its risk of bias and was therefore deemed of good quality. The study demonstrated 'low' risk of bias assessments across each domain: the participants were representative of the target population, the participants were allocated to each treatment group by blocked randomization, the participants and investigators were blinded to the allocation of interventions, those involved in measuring the study outcomes were unaware of the type of intervention received, there were equal attrition rates between the intervention groups, and all outcomes were reported. Please refer to Table 5 in Appendix II for the complete risk of bias entry for the Fard et al. (2017) study.

The second randomized controlled trial by Hantsoo et al. (2014) investigated the comparison between sertraline to a placebo for treating postpartum depression. This study had a majority of 'low' assessment for risk of bias; however, it was judged as 'high' risk of bias for two of the domains. Therefore, this study was deemed of fair quality. The 'high' risk of bias judgment was demonstrated in the selection bias and attrition bias entries. The selection bias was judged as a 'high' risk because there was an unequal distribution of participants between the two intervention groups. The attrition bias was judged as a 'high' risk because the majority of the participants who failed to complete the study were those from the placebo group and there was

one accidental case of unblinding. Please refer to Table 6 in Appendix II for the complete risk of bias entry for the Hantsoo et al. (2014) study.

The Singata-Madiliki et al. (2016) study investigated the effects of DMPA (a hormonal contraceptive) on postnatal depression. This study had an overall 'low' assessment for its risk of bias and therefore, this study was deemed of good quality. Similar to Fard et al. (2017), this study demonstrated 'low' risk of bias assessments across each domain (selection bias, allocation bias, performance bias, detection bias, attrition bias, and reporting bias). Please refer to Table 7 in Appendix II for the complete risk of bias entry for the Singata-Madiliki et al. (2016) study

Lastly, the Sunder et al. (2004) study investigated the efficacy of sertraline versus placebo for the prevention of recurrent postpartum major depressive disorder. This study had a majority of 'high' and 'unclear' assessments for risk of bias, with only one domain being judged as 'low' risk and therefore, this study was deemed of poor quality. The 'high' risk judgements were demonstrated in the selection bias, detection bias, and attrition bias entries. There was a high risk for selection bias because the study explained very little detail as to the methods used to recruit the participants. There was a high risk for detection bias because key personnel involved in the study were not blinded to the allocation of intervention processes. There was a high risk for attrition bias because there was an unequal distribution of participants between the interventions, unequal number of participants lost to follow-up, and there was a very small number of individuals who eventually participated in the study. The 'unclear' risk judgements were demonstrated in the allocation bias and performance bias entries. There was an unclear risk for allocation bias because there was no mention as to how the interventions were allocated between the groups. There was an unclear risk for performance bias because there was no indication as to

whether or not the participants were blinded to the intervention they received. Please refer to Table 8 in Appendix II for the complete risk of bias entry for the Sunder et al. (2004) study.

**b) Cohort and literature reviews**

The quality of the ten cohort studies and eleven literature reviews included in this systematic review were assessed by using the Critical Appraisal Skills Programme checklist. These checklists target three main categories for assessing the quality of each study: are the results of the study valid? What are the results? And will the results help locally? The CASP checklist for cohort studies contains 12 questions and the checklist for literature reviews contains 10 questions. The answers to the questions can either be yes/can't tell/no and with the option to add any notable comments in order to support the answer given. A summary of the checklist results is described in the following section, beginning with the cohort studies.

*i. Cohort studies*

The Alibekova et al. (2016) study investigated the effects of smoking on maternal perinatal depression. The majority of the answers were marked as 'yes' in the checklist; however, there were some answers marked as 'no'. The cohort was noted to not have been recruited in an acceptable way as the recruitment took place across five different hospitals and there is the presence of selection bias based on consecutive sampling and the individuals could participate in the study voluntarily. It was also noted that the results could not be applied to the local population (Ottawa, Canada) as the participants in this study were from Taiwan and could be considered as being sufficiently different from the population of Ottawa. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of satisfactory quality (recognition of selection bias).

The Dagher and Shenassa (2012) study investigated the association between cigarette smoking and vitamin intake during pregnancy with postpartum symptoms eight weeks after childbirth. Their checklist answers varied across all sections. There were some answers marked as 'can't tell' because there was not a lot of information regarding how the investigators measured the outcomes, other than that they conducted hospital and home interviews, so it was difficult to determine whether or not the outcome was accurately measured to minimize bias. The investigators did mention confounding factors; however, there were no details as to what types of "stress-related" and "perinatal" factors they were referring to when they described them as confounders. Additionally, it was difficult to determine if the results could be applied to the local population because there was no mention of which city/state in the United States where they recruited the participants, therefore the local setting could be much different than that of the study. There were a few answers marked as 'no' because the cohort was noted to not have been recruited in an acceptable way as the participants were recruited from a single hospital site and can therefore only be generalizable to a population with similar demographic characteristics. The exposure was noted to not have been accurately reported to minimize bias as there was no mention of how smoking status and intake of other substances were measured; however, the questions posed by the investigators are reported in a table. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of satisfactory quality.

The Frandsen et al. (2017) study investigated the comparison between demographic and antenatal characteristics of women who smoke during pregnancy to those who did not. Their checklist answers were not as favorable as the other cohort studies. There was one answer marked as 'can't tell' because the methods used to measure the outcomes were not entirely clear,

which in turn, contributed to the potential for bias. The majority of the answers were marked as ‘no’ because the investigators did not identify any important confounding factors and therefore, were not considered in the study’s design and/or analysis, the follow-up of participants was not complete enough nor was it long enough, the authors did not provide any range of confidence intervals to determine the preciseness of the results, and the results cannot be applied to the local population as this study was conducted in Tasmania with a variety of different sociodemographic characteristics in their maternal populations compared to local Canadians. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of poor quality.

The Khan et al. (2015) study investigated prenatal second-hand smoke exposure and the risk for postpartum depression. Their checklist varied in their answers, however, most of them were marked as ‘yes’. There were a few answers marked as ‘can’t tell’ because it was difficult to determine if the participants were recruited in an acceptable way as they were representative of a defined population, but the investigators state the presence of selection bias in the study due to a relatively low response rate (59-72%). Additionally, it was not apparent in the completeness of the follow-up of subjects as there was very little detail provided in their characteristics (which could have been pertinent to the study given the study objectives). There was one answer marked as ‘no’ because their outcome measurements were not entirely accurate, since the investigators measured the outcome by only asking the participants two questions and they did not use a reliable system (ex: EPDS) – their measurements did not prompt to provide information on the duration or intensity of the postpartum depressive symptoms. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of satisfactory quality.

The Mbah et al. (2013) study investigated the exposure of environmental tobacco smoke and the risk of antenatal depression. Their checklist answers were primarily marked as 'yes', with only a few answers marked as 'can't tell'. This was due to the inability to determine if the investigators considered any confounding factors in their design or analysis, if the follow up of subjects were complete enough, if the follow up of subjects was long enough, and if the results of the study fit with any other available evidence, since the study only reflects on other background information but does not report much evidence from other studies reflecting their current findings. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of adequate quality.

The Munafò et al. (2008) study investigated the relationship between smoking status during pregnancy and postnatal depressive symptoms. Their checklist was marked primarily with 'yes' answers, with few answers marked as 'no'. This was due to the evaluation of their follow-up of subjects not being complete enough, as they lost approximately 40% of their starting sample and even those who remained participants provided a considerable, although incomplete, amount of information. The results of the study are not applicable to the local population as this study was conducted in the United Kingdom some years ago and therefore the population could be considered much different than in Canada, in addition to the majority of the exclusions being related to a further pregnancy during the measurement period which in turn could affect the generalizability of the results. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of good quality.

The Salimi et al. (2015) study investigated the relationship between perinatal cigarette smoking and postpartum depression. Their checklist had a variety of answers, of which primarily being 'yes'. There were answers marked as 'can't tell' because it was unclear if the follow-up of

subjects was complete enough and if it was long enough. There were answers marked as ‘no’ because the outcome measurement was not entire accurate since the investigators screened for postpartum depression by only asking the participants two questions and therefore they did not use a reliable measurement system (ex: EPDS). The investigators also did not identify any important confounding factors in the study. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of satisfactory quality.

The Sheffield et al. (2018) study investigated the association between particulate air pollution exposure during pregnancy and postpartum maternal psychological functioning. Their checklist had a variety of answers, which were not all favorable. There were answers marked as ‘can’t tell’ because it was unclear if the follow-up of subjects was complete enough and if it was long enough. It was also difficult to determine if the results of the study fit with other available evidence because more studies are needed in order to replicate these findings in other populations, particularly with respect to potential windows of vulnerability for women during pregnancy. There were answers marked as ‘no’ because there was the presence of selection bias, since the investigators leveraged an ethnically diverse, lower income urban cohort of pregnant women, they did not identify all important confounding factors (they missed exposures to other potential pollutants and chemicals), and they did not identify any implications of this study for practice. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of poor quality.

The Song et al. (2018) study investigated passive smoke exposure and postpartum depression. Their checklist had a variety of answers. There were answers marked as ‘can’t tell’ because it was unclear if the exposure was accurately measured to minimize bias since the investigators only refer to a “specially designed questionnaire” when they collected data on

smoking status. Additionally, the investigators do mention that confounders were considered in the analysis; however, it was unclear as to whether they were indeed included in the analysis (i.e. which techniques were used). There were answers marked as 'no' because the investigators do not identify any important confounding factors (although they mention their consideration in the analysis), the follow-up of participants was deemed not complete enough, and the results cannot be applied to the local population as this study was conducted in China, with a variety of different sociodemographic compared to Canada. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of adequate quality.

Lastly, the Underwood et al. (2017) study investigated a variety of risk factors during the prenatal period for development of postnatal depression. Their checklist had a variety of answers; however, the majority were marked as 'yes'. There were some answers marked as 'no' because the investigators did not identify any important confounding factors and were in turn, not considered in the study's design and/or analysis. Additionally, the results cannot be applied to the local population as this study was conducted in New Zealand which has different sociodemographic characteristics compared to Canada. Notably, this checklist contains a different response to one of the questions compared to the other cohort CASP checklists, which is an answer marked as 'no' to the question "do you believe the results?" This was marked 'no' because as the evaluator, it was found that other studies included in this systematic review have found an association between antenatal smoking and postpartum depression, while this study by Underwood et al. (2017) did not find an association. This finding could also support the answer to the question regarding the population of the study being different than that of the local population and that the results in turn, cannot be applied to this Canadian population. Based on

the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of adequate quality.

*ii. Literature reviews*

The quality assessments of the literature reviews were completed by using a CASP checklist as well. This checklist contains the same three categories over 10 questions in total, however, the questions in this checklist are more specific to literature reviews. These questions address the validity of the included studies, the level of the quality assessment of the included studies, and overall results of the included studies. The studies evaluated as being of good quality include those where the investigators address a clearly focused research question, they include the appropriate type of papers for the review, all relevant studies seem to be included in the review, the investigators perform an appropriate quality assessment of the included studies, all important outcomes are considered, the results can be applied to the local population and the overall results of the study are definite and clearly expressed.

The Chen et al. (2018) study investigated the relationship between prenatal smoking and postpartum depression. Their checklist was very favorable, in that majority the answers were marked as 'yes'. There was one answer marked as 'can't tell' because it was unclear to determine the characteristics of the populations of the included studies and only two of the studies were from Canada. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of good quality.

The Coletta et al. (2010) study investigated omega-3 fatty acid intake during pregnancy. Their checklist had a variety of answers. There were answers marked as 'can't tell' because the investigators did not list the databases used for the literature review and therefore it is unclear if all relevant studies were included, there was no mention of any quality assessment, and it was

difficult to determine if the results could be applied to the local population as the review contained an variety in the types of studies included and there was little detail in their description. There was one answer marked as ‘no’ because the results of the review were not combined, since the investigators simply presented the results from the included studies in a narrative format and the results of the studies were not displayed very clearly. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of poor quality.

The Derbyshire and Costarelli (2008) study investigated dietary factors implicated in the etiology of postnatal depression. Their checklist had a variety of answers. There was one answer marked as ‘can’t tell’ because there was not enough detail in the characteristics of the populations across the studies and therefore it is unclear if the results could be applied to the local population. There were some answers marked as ‘no’ because the investigators did not include all relevant studies since they only used one online database to search the literature and the investigators did not perform any quality assessments. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of satisfactory quality.

The Ellsworth-Bowers and Corwin (2012) study investigated the link between micronutrient status and postpartum depression. Their checklist had a variety of answers. There was one answer marked as ‘can’t tell’ because there was not enough detail in the characteristics of the populations across the studies and therefore it is unclear if the results could be applied to the local population. There were some answers marked as ‘no’ because the investigators did not include all relevant studies since they only used one online database to search the literature and the investigators did not perform any quality assessments. Based on the results of the CASP

checklist and the assessment for the risk of bias, this study could be considered of satisfactory quality.

The Freeman (2006) study investigated omega-3 fatty acid intake and perinatal depression. This checklist had a variety of answers. There was one answer marked as 'can't tell' because there was not enough detail in the characteristics of the populations across the studies and therefore it is unclear if the results could be applied to the local population. There were some answers marked as 'no' because the investigator did not perform any quality assessments and they did not include all relevant studies since they only used one online database and a manual search. Although even with this search strategy, they did not expand on any additional online databases to search the literature. Additionally, the results were not presented very clearly since the review only included one Results table for the included studies and there was no further mention of the total number of studies included in the review (the findings were simply stated in a narrative format). Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of poor quality.

The Glenville (2006) study investigated nutritional supplement intake during pregnancy and maternal health. This checklist had a variety of answers. The majority of the answers were marked as 'can't tell' because it was unclear if all the relevant studies were included since the investigator did not identify the databases/search strategy used for the review, there was not enough detail in the characteristics of the populations across the studies and therefore it is unclear if the results could be applied to the local population, and with the findings presented pertaining to only one nutritional supplement and postpartum depression, it is difficult to conclude if the benefits are worth the cost for further studies. There was one answer marked as 'no' because the investigator did not conduct any quality assessments. Based on the results of the

CASP checklist and the assessment for the risk of bias, this study could be considered of poor quality.

The Howard et al. (2005) study investigated the use of antidepressants in the prevention of postpartum depression. Their checklist contained only a few unfavorable answers. There were answers marked as 'can't tell' because the investigators did not identify the databases used for the review, they only mention the use of "CCDACTR studies" (no further description as to what those are) therefore it is unclear if all important studies were included. It was also difficult to determine if the results could be applied to the local population as the investigators did not provide any characteristics of the populations of the included studies. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of satisfactory quality.

The Leung and Kaplan (2009) study investigated the role of nutrition in perinatal depression. Their checklist had a variety of answers. There were a few answers marked as 'can't tell' because the investigators did not identify the databases used in the review, nor were any inclusion/exclusion criteria provided, therefore it was unclear if all relevant studies were included; and it was difficult to determine if the results could be applied to the local population as the investigators did not provide any characteristics of the populations of the included studies. There was one answer marked as 'no' because the investigators did not perform any quality assessments. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of poor quality.

The Molyneaux et al. (2018) study investigated the use of antidepressants in the prevention of postpartum depression. Their checklist was evaluated quite favorably as the majority of the answers were marked as 'yes'. There were a few answers marked as 'can't tell' because it was

difficult to determine if the results could be applied to the local population as the investigators did not provide any characteristics of the populations of the included studies and it is difficult to determine if the benefits are worth the harms/costs because more research is needed in this area in order to determine the true benefit of antidepressants in preventing postpartum depression. Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of good quality.

The Pariser et al. (1997) study investigated clinical perspectives of postpartum mood disorders. Their checklist had a variety of answers and was evaluated with uncertainty. There were some answers marked as 'can't tell' because it was difficult to determine if the authors searched for the right type of papers as they presented the findings in a narrative format and there was no further mention of the included studies' design; there was no mention of any databases used for the review, therefore it was unclear if all relevant studies were included. Additionally, the investigators did not provide any participant characteristics from the included studies, therefore it was unclear if the results could be applied to the local population (this study was also conducted more than 10 years ago, so it is very unlikely in any case). Based on the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of poor quality.

Lastly, the Sparling et al. (2017) study investigated the role of diet and nutritional supplementation in perinatal depression. Their checklist was evaluated very favorably as the majority of the answers were marked as 'yes'. There was one answer marked as 'can't tell' because the investigators did not provide any participant characteristics from the included studies, therefore it was unclear if the results could be applied to the local population. Based on

the results of the CASP checklist and the assessment for the risk of bias, this study could be considered of good quality.

**c) Cross-sectional studies**

The quality of the five cross-sectional studies included in this systematic review were assessed by using the Downs and Black Checklist (1998). This quality assessment tool is a 27-item checklist with the options of answering yes/no/unable to determine for each question.

Firstly, the Kalayasiri et al. (2018) study investigated the effects of exposure to second-hand smoke on the quality of life of postpartum women. In terms of their checklist, those questions relating to study quality had answers marked as 'no' because the study did not list any cofounders, the study did not report any adverse events, nor were any descriptive characteristics given of loss of patients to follow-up. For those questions relating to external validity, all questions were marked as 'yes'. For those questions relating to internal validity, there were answers marked as 'no' because there was no mention of 'data dredging', no randomization to intervention groups, no concealment of interventions, and no adjustment for confounders. There were answers marked as 'unable to determine' because there was no mention of blinding subjects to intervention, no mention of blinding those who measured the outcomes, no mention of compliance to the inventions, and no mention if patients lost to follow-up were considered. The 'no' and 'unable to determine' answers were expected for those questions relating to randomization and blinding processes, based on the study design of Kalayasiri et al. (2018) as this is not a randomized controlled trial and cross-sectional studies do not consider those study parameters. The Downs and Black (1998) checklist can also be used to assess the quality of those types of study designs however for this systematic review, another type of quality assessment was used (Cochrane Risk of Bias tool). As mentioned in the checklist itself, it states that "all

non-randomized studies should be answered ‘no’ for those questions of randomization measures (Downs & Black, 1998). Therefore, given these results and a checklist score of 14/31 (0 points for those questions favouring randomized controlled trials), the overall quality assessment of this study is of adequate quality.

The Vivilaki et al. (2016) study investigated the exposure of environmental tobacco smoke among a sample of pregnant women. In terms of their checklist, those questions relating to study quality had answers marked as ‘no’ because no adverse events were reported, no characteristics of patients lost to follow-up were mentioned, and the probability values were not reported. For those questions relating to external validity, all answers were marked as ‘yes’. For those questions relating to internal validity, there were answers marked as ‘no’ because there were no blinding measures, no mention of ‘data dredging’, no further randomization measures (which is expected based on this study design as previously mentioned), and no mention of whether patients lost to follow-up were considered. Therefore, given these results and a checklist score of 16/31 (0 points for those questions favouring randomized controlled trials), the overall quality assessment of this study is of good quality.

The Wang et al. (2018) study investigated exposure to third-hand smoke during pregnancy and the risk of postpartum depression. In terms of their checklist, those questions relating to study quality had answers marked as ‘no’ because the characteristics of the patients included in the study were not described, no confounders were provided, and adverse events were not considered. For those questions relating to external validity, there was an answer marked as ‘no’ because the participants were not seen to be representative of the entire population from which they were recruited. As noted during the recruitment process, not all women who gave birth in the hospital came back to the same hospital for their postpartum

checkup in order to complete the questionnaire. For those questions relating to internal validity, there were answers marked as ‘no’ because there were no blinding measures for this study, no mention of ‘data dredging’, and no randomization measures were used (as expected). There was an answer marked as ‘unable to determine’ because there was no mention of adjustment for confounders. Therefore, given these results and a checklist score of 16/31 (0 points for those questions favouring randomized controlled trials), the overall quality assessment of this study is of good quality.

The Weng et al. (2016) study investigated the effects of tobacco exposure on perinatal depression. In terms of their checklist, those questions relating to study quality had answers marked as ‘no’ because adverse events were not mentioned in the study and the characteristics of the patients lost to follow-up were not described. However, there was an answer marked as ‘yes’ which is different from the other checklists in that this study did describe the principal confounders in each group of participants (worthy of 2 points). For those questions relating to external validity, all answers were marked ‘yes’. For those questions relating to internal validity, there were answers marked as ‘no’ because there was no mention of ‘data dredging’, no adjustment for confounders in analyses, no blinding measures were used, and no randomization measures were used (as expected). Therefore, given these results and a checklist score of 17/31 (0 points for those questions favouring randomized controlled trials), the overall quality assessment of this study is of good quality.

Finally, the Yalçin et al. (2015) study investigated organochlorine pesticide exposure and maternal psychopathologies. In terms of their checklist, those questions relating to study quality had answers marked as ‘no’ because the characteristics of patients included in the study were not described, cofounders were not mentioned, adverse events were not considered, and the

characteristics of participants lost to follow-up were not described. For those questions relating to external validity, there were answers marked as 'no' because the participants were not representative of the entire population from which they were recruited (primarily from a suburban area with no known exposure). For those questions relating to internal validity, there were answers marked as 'no' because there was no mention of 'data dredging', the participants lost to follow-up were not considered, and there were no randomization and blinding measures (as expected). There was an answer marked as 'unable to determine' to the question asking if the compliance to intervention was reliable. However, there was an answer marked as 'yes' which is different from the other checklists in that this study's analyses did adjust for the different lengths of follow-up of participants. Therefore, given these results and a checklist score of 12/31 (0 points for those questions favouring randomized controlled trials), the overall quality assessment of this study is of poor quality.

**IV) Interdisciplinary Perspectives**

**a) Environmental toxicology**

Environmental toxicology research has changed over time and is gathering more and more attention. Scientific research is always changing, as more research begins to focus on these environmental areas and investigators continue to consider toxicants and contaminants and their impact on health. If we were to compare the amount of research concerning environmental toxicology that there was 25 years ago to the amount that is currently available on an online database, the results are remarkable. A simple search on PubMed (Medline) (a well-known and commonly used database for scientific research and one of the databases used for this systematic review), using the search term, 'environmental toxicology' for articles published in 1994-1995,

produces a total of 1,069 articles. Using the same search criteria, but changing the year of publication to 1994-2019, this search produces 42,767 articles. This number will continue to increase; the importance resides in determining the most efficient method to measure toxicant exposure levels, in order to limit harmful and potentially long-term effects on human health.

An article by Fairbrother et al. (2019) contributes to the discussion relating to this field of research by identifying important environmental quality research questions in North America as part of a global initiative. The Global Horizon Scanning Project (GHSP) was launched in 2013 to identify key research questions that could make significant advances toward more sustainable environmental quality over the next decade. These authors specifically engaged North American individuals representing multiple sectors (business, academia, government) of the Society of Environmental Toxicology and Chemistry (SETAC), and the American Chemical Society's (ACS) Environmental Chemistry (ENVR) and Agrochemicals (AGRO) divisions (Fairbrother et al., 2019). They solicited research questions from these scientists and engineers, which was followed by a synthesis workshop in which the top research questions were identified and ranked into several interconnected themes. One of the themes included 'Addressing environmental analytical chemistry challenges in the 21st century', which derived research questions focusing on how to develop quantitative analytical methods for next-generation emerging contaminants; how to develop advanced forensics (e.g. chemical fingerprints) for tracing and modelling the sources of contaminants, which could address challenges such as identifying sources of contaminants from activities like fracking, accidents (e.g. oil spills), or long-range transport of atmospheric emissions; and also, how to better describe and predict the fate of chemical species during waste treatment, recycling, and disposal, especially emerging chemicals, to support decision making (Fairbrother et al., 2019).

Another relevant theme included ‘Enhancing prediction of chemical exposure in environmental assessments’, which derived research questions focusing on chemical exposure models, their sources of uncertainty, and what data should be collected to reduce uncertainty related to chemical properties and process rates, emissions data, and spatial and temporal variability within the environment (Fairbrother et al., 2019).

A third theme included ‘Challenges and approaches to addressing multiple stressor interactions’, which derived research questions focusing on inorganic and organic toxicants, pesticides, and POPs; the scientists and engineers anticipated that POPs, currently sequestered in the cryosphere (part of the Earth’s surface that is frozen for some of the year), will be released as ice melts and permafrost thaws (Fairbrother et al., 2019). As climate change continues to be a centre of discussion amongst the scientific/environmentalist community, it is these areas of concern where researchers need to direct their attention and investigations in order to target issues and anticipate the consequences.

With reference to human health, another theme from Fairbrother et al. (2019) included ‘Anticipating and predicting human and ecological impacts of chemicals’, which derived research questions focusing on the need to design chemicals and predict their properties and biological activities in an effort to minimize environmental and human health hazards, and the necessity to coordinate across disciplines and sectors in order to increase our understanding of environmental exposures and adverse ecological or health outcomes in the field and in local communities. The latter highlights the importance of using an interdisciplinary approach in addressing these environmental issues surrounding human health because there exist a variety of socioeconomic properties among various populations around the world, with different degrees of

exposure to all sorts of toxicants, and through combining knowledge from multiple disciplines in the research, the results will be more pertinent to minimizing effects on health.

The final theme relevant to the topic of this review included 'Risk assessment and communication and at the science-society interface', which derived questions focusing on pesticides, and how research continues to be needed to inform pesticide development for large-scale, sustainable agriculture to find chemistries that specifically target pests without affecting non-target species, and that a holistic program in agroecology research should include methods for efficient water use, reduced energy inputs (e.g., fertilizers) and use (e.g., tractors), and proper waste disposal (e.g., manure from feedlots) (Fairbrother et al., 2019). Additionally, appreciating and understanding the social systems within which farmers work will enable sustainable agriculture on a scale sufficient to feed a growing world population in the face of a rapidly changing climate (Altieri, 2018).

These constructed research questions provide appropriate and significant directions for future environmental research, while guiding attention towards toxicological effects on various aspects of health.

**b) Psychology and postpartum depression**

Another key component representing the interdisciplinarity of this systematic review is its focus on psychology and postpartum depression. As previously discussed, there exists a multitude of various risk factors for postpartum depression, with the central focus on biological and psychosocial aspects in the literature. This review can be distinguished from the norm, as demonstrated in its objective to investigate whether there were any non-physiological risk factors explored in the literature pertaining to the development of postpartum depression. The inclusion of these toxicants as risk factors for postpartum depression, as part of this review, contributes to

their increasing recognition as risk factors in other scientific literature. Evidence in the recent medical literature confirms that individual and public health are being threatened by chemical exposures (Genuis, 2009). Of these recent publications there exists growing evidence on the dangers of toxicants including neurotoxins that compromise normal development, endocrine disruptors that modify hormonal action and beyond, chemical mycotoxins with potential to suppress immune function, and industrial agents with countless pathological mechanisms of harm including carcinogenicity (Genius, 2009). Studies have found that assorted pharmaceutical agents can alter brain chemistry and provoke pathological behaviour - antivirals such as ribavirin and interferon, for example, can induce profound depression (Kumar & Gupta, 2007), while pediatric SSRI use has been linked to aggression and self-destructive behaviour in some cases (Sibbald, 2004).

There is evidence confirming that some other chemical agents found in the environment have the potential to induce pathological change in mental function, as demonstrated in a case study by Genius (2009). A 24-year old primary school teacher complained of fatigue, depression, and disturbed thinking and was referred to a physician trained in environmental medicine. A detailed chronological history revealed that the patient last felt well about 24 months previously at which time he began to experience worsening depression, insomnia, and obsessive-compulsive tendencies. Additionally, he complained of increasing anxiety and frequent intrusive ideation of inflicting harm on students within his elementary school class. He was reluctant to disclose his thoughts to friends or family and it was at this point when he confided in a counselor and was immediately referred to a psychologist. Various themes were explored in therapy (e.g. troubled childhood, alleged spiritual conflicts, etc.) but despite these intense therapy sessions, his mood and thought fixation persisted. A family physician then instituted therapy with SSRI

antidepressants, which, after many weeks of increasing doses, made little difference to his depression or intrusive thoughts. More pharmacotherapies were administered, however, the patient experienced assorted side effects (e.g. weight gain, persistent nightmares, debilitating drowsiness, etc.). With no family history of mental health problems, the patient questioned the "inborn chemical imbalance" label and was devastated to hear he had a chronic mental illness which required lifelong medication. However, a detailed exposure assessment (developed by the Ontario College of Family Physicians) followed by a red blood cell toxicological metal screen revealed high levels of mercury, likely originating from his considerable intake of canned tuna. Three years earlier, the patient read that essential fatty acid consumption through dietary fish was beneficial for brain function, which in turn, led to daily ingestion of one or two cans of tuna fish. Dietary intake alongside recent World Health Organization reports identifying seafood as a leading cause of mercury exposure (Bigham, Copes, & Srour, 2002), provided the indication for metal screening. Based on the patient's history of considerable ongoing tuna consumption and his associated laboratory findings, subsequent clinical discussion included options for detoxification of accumulated mercury as mercury is known to accumulate in the brain tissue (Guzzi et al., 2006) and to act as a neurotoxin; blood levels of toxic metals (an indication of recent exposure) often underestimate mercury bioaccumulation within the tissues (Head, 2002).

This case study by Genuis (2009) supports the notion of supplemental factors contributing to the risk of developing mental health conditions as it is possible for exposures to have been ongoing for many years prior to be the manifestation of an accumulation of the toxicants. This case study further supports the concept that biological processes underlie mood and thought - as a physical organ, the brain can respond to physical determinants of disease with manifestations

typical of brain pathology and in this case, includes depression, anxiety, altered thinking and behaviour, and insomnia, to name a few (Genuis, 2009).

**c) Methodology**

Lastly, a major component representing the interdisciplinarity of this thesis project is recognized in its methodology as a systematic review. This type of methodology makes it possible to conduct interdisciplinary research, by identifying associations between different disciplines, in order to determine the extent of the types of studies investigating similar topics and the degree to which they overlap. It's important to consider the concept of interdisciplinary research through the means of a systematic review, as it allows the advancement of knowledge and understanding of various disciplines and fields of research, including mental health and the environment. Systematic reviews were initially used to combine information from more than one comparative study, usually RCTs that were individually underpowered or as a group failed to produce consistent or conclusive findings (McCall & Connor, 2010). Systematic review methods evolved to incorporate a range of other study types, such as cohort and case-control studies. This type of approach aims to objectively collect, combine, and summarize all the available information/literature, compared to a traditional narrative approach where the conclusions may be unjustified (McCall & Connor, 2010). A fundamental goal in using this type of methodology in scientific research is to close the apparent knowledge gaps in certain fields of research, for example, relating to maternal mental health and its associating risk factors and in order to do so, systematic research must be promoted (especially in low-resource areas) and research findings must be made visible, available, and accessible (Chapman et al., 2013). Through the evolution of including qualitative research in systematic reviews, these methods are able to improve the understanding about health beliefs and behaviours, all of which play a significant role in health

education and awareness surrounding mental health topics. Gaps in knowledge can be bridged and specific to our interests, maternal mental health outcomes may be improved with research production and utilization through evidence-based policy and practice (Chapman et al., 2013).

**V) Recommendations and Implications for future research**

The overall results from the included studies in this review demonstrate that environmental toxicant exposure in the prenatal/perinatal period does present as a risk factor for developing postpartum depression. However, the majority of the included studies investigated cigarette/tobacco smoke exposure, while there were only few on other environmental exposure, such as pesticides and particulate air matter. Future research in this field should direct more focus on these airborne toxicants and their effects on mental health. As previously noted, the challenge lies in determining the necessary measures needed to predict and estimate exposure levels for populations at higher risk. There are key components required in order to efficiently approach these next steps, of which include the need for directed research to take advantage of today's vast network of electronic communication mechanisms to enable timely and sustainable communication across the wide range of disciplines that support environmental science and regulatory decision-making (Hurd, 2000). Through conducting systematic reviews, it will be possible to disseminate the current findings surrounding environmental toxicology and its effect on not only physiological health, but also mental health, as this methodology serves to incorporate studies across a vast range of disciplines and can help provide insight on how the environment reflects on each of them.

**a) Canadian Policies and Regulations**

*i. Environment Canada*

It's important to consider and acknowledge the various policies and regulations implemented by the Canadian Government, in order to become familiar with what they are doing in terms of the procedures and practices in targeting daily environmental issues. Environment Canada administers over a dozen Acts of Parliament, either in whole or in part, and is responsible for meeting numerous obligations spelled out in legislation ("Environment and Climate Change", 2017). Under its various acts, the Department works to address and report a wide range of complex environmental issues, including: monitoring air and water quality and emissions of greenhouse gases, controlling the level of toxic substances in commercial products, consulting with Canadians, regulated stakeholders, researchers, and governments, researching and protecting the habitat of species at risk, permitting and when necessary, preventing international trade of hazardous waste, hazardous recyclable materials and endangered species, and finally, promoting, inspecting and enforcing regulatory requirements ("Environment and Climate Change", 2017).

*ii. Canadian Environmental Protection Act (CEPA)*

As part of Pollution Prevention, Environment Canada enacted the Canadian Environmental Protection Act (CEPA) of 1999. The primary purpose of CEPA is to contribute to sustainable development through pollution prevention, providing a legislative basis for a range of federal environmental and health protection programs ("Understanding the Canadian Environmental Protection Act", 2019). These include activities related to: the assessment and management of risks from chemicals, polymers, and living organisms, programs related to air and water pollution, hazardous waste, air pollutant and greenhouse gas emissions, ocean disposal, and

environmental emergencies ("Understanding the Canadian...", 2019). Under section 44 of the Act, the Minister of the Environment is authorized to: establish environmental monitoring stations, collect and publish data on environmental quality in Canada, conduct research and studies on pollution control and environmental contamination, formulate pollution prevention plans, and publish information on these plans and on the quality and state of the environment in Canada ("Understanding the Canadian…", 2019). The monitoring network under this Act publishes the information relating to these programs such as national air pollution surveillance program, greenhouse gas measurement program, chemicals management program, etc. This Act allows the reporting of pertinent information regarding various environmental indicators, such as air indicators (air quality, air pollutant emissions, etc.), and climate indicators (greenhouse gas emissions), water indicators (water quality, phosphorus levels, mercury, lead, etc.). The webpages on all of these various environmental indicators exhibit an abundance of reports, policies, and data pertaining to the different examinations and observations of how each of these indicators are impacting the environment across Canada, all of which are very informative and notably updated.

*iii. Health Canada*

Another key department within our Federal Government is Health Canada, and, in their statement, they recognize a responsibility for helping Canadians maintain and improve their health, by ensuring that high-quality health services are accessible, and they work to reduce health risks (Health Canada, 2019). Among the numerous services provided on their website, they include information regarding 'Environmental and workplace health'. The section offers information and advice on some of the most common environmental factors as identified by Health Canada, that affect human health: air, nose, soil and water pollution, climate change,

environmental contaminants, occupational health and safety, pest control, and radiation (Health Canada, 2004). By providing and displaying this vast information pertaining to the environmental and health, Health Canada aims to protect the health of Canadians from environmental risks (Health Canada, 2004). The subjects for this section contain and are not limited to: air quality, environmental contaminants (i.e. lead, BPA, dioxins and furans), radiation (radon, UV, x-rays) fuels and air pollution, formaldehyde, and environmental assessment. In the environmental contaminant category, Health Canada states that they work jointly with Environment Canada to assess potential risks to human health posed by new and existing substances in Canada under the CEPA, 1999.

Health Canada provides information relating to exposure and health effects of various chemicals and pollutants (e.g. carbon monoxide, BPA, lead, pesticides, tobacco, VOCs, etc.), identifying the types of exposure, potential health risks, potential health effects, and ways of reducing risks. Interestingly, when listing the potential health effects, they mention 'effects on the mental, intellectual or physical development of children' (Health Canada, 2012). No additional information is displayed or available on the webpage, nor is there any mention of mental health effects of other populations. Furthermore, the Government of Canada launched the Chemicals Management Plan (2006) to protect Canadians and their environmental from the harmful effects of chemical substances. The Minister of Health and the Minister of Environment and Climate change have committed to addressing the remaining 1550 priority chemicals out of the original 4300 identified chemicals by 2020 (Health Canada "CMP," 2006). The Chemicals Management Plan (CMP) builds on previous initiatives by assessing chemicals used in Canada and by taking action on chemicals found to be harmful to human health and/or the environment (Health Canada "CMP," 2006). This plan provides short fact sheets about chemical substances,

information on CMP science committees and stakeholder advisory councils and panels, CMP initiatives, latest news from the past few years relating to these chemicals, CMP progress reports in order to keep stakeholders and interested parties up to date on the activities and programs related to CMP, risk assessments, and risk management process.

In reference to human health, Health Canada aims to prevent health problems by educating the public on drugs, diseases and more, through their 'Health Concerns' section of their online portfolio. Subjects include but are not limited to: alcohol, controlled substances (i.e. street drugs) and precursor chemicals (e.g. flavouring agents), diseases and conditions, drug prevention and treatment, tobacco, and violence and abuse. This section provides information on measures Health Canada is taking to prevent the production of illicit drugs, various health conditions and their symptoms and treatments, the hazards of illicit drug use and the risk that drugs pose to the health of the family and community as well as promoting awareness of how greatly smoking affects health (Health Canada "Health Concerns," 2009). In the 'diseases and conditions' subject, there is a subsequent 'mental and behavioural' component which lists various services and information on the topic. Among those services is a webpage on mental illness and more specifically, information on depression. This webpage describes what depression is, listing the associating symptoms, and does in fact mention perinatal depression as a type of depressive mood disorder. However, the explicit detail surrounding depression and its causes/symptoms is primarily centered on major depressive disorder. Additionally, there is a service pertaining to cannabis and mental health and on this webpage, they describe how cannabis is a risk factor for other mental illnesses such as psychosis and schizophrenia, with a main focus on the health effects of cannabis use on youth populations (Health Canada "Cannabis," 2018).

**b) In brief**

Based on the current information and services available from Health Canada and Environment Canada, there seems to be an immense amount of knowledge and material regarding the environment and contaminants/toxicants that can be found, the Acts and policies relating to each environmental aspect, and the various actions the Government has made and continues to make on the matter. However, even with the informative sections pertaining to the environment and mental health, the departments do not acknowledge the emerging association between the two as there is little information regarding exposure to xenobiotics/ toxicants and the development of mental health disorders. When discussing harmful chemicals and potential health effects, that section does mention the effects that these chemicals may have on the mental development of the children but does not present any additional information on the effects of any other population nor does it provide any supporting documents. Furthermore, with all of this available and accessible information provided by the Government of Canada, there needs to be more attention directed towards these reports and services so that healthcare workers such as health practitioners and other health professionals can advise and promote these policies and implement these regulations into their practice. Health professionals and other officials should consider toxicant exposure and adverse chemical accumulation as a potential determinant when individuals present with inexplicable mental health problems or disordered behavior (Genuis, 2009). Emerging environmental health recommendations should encourage primary care practitioners as well as specialists to incorporate exposure assessment tools when the etiology of medical afflictions, including mental health disorders, remains uncertain (Weir, 2002).

Ultimately, as our health continues to be affected by increasing exposure to environmental toxicants, health practitioners should consider toxicological factors and

incorporation of exposure assessment tools when encountering patients with mental health complaints because as much as the environment is changing, the way and manner our bodies react to these changes becomes important to consider.

**VI) Strengths and Limitations**

There were some apparent limitations to this systematic review. Firstly, this review did not include studies published in other languages and therefore did not consider non-English articles pertaining to this topic. This review was limited to the five online databases used in searching the literature for relevant articles and although this can be seen as a decently diverse group of databases, there are many more databases available to use but were otherwise not considered. This review primarily included non-randomized studies (87%) while there were only a few randomized controlled trials (13%), which therefore established heterogeneity among the included studies. Additionally, a meta-analysis was not performed for this systematic review and therefore the results from the four randomized-controlled trials were not combined to give an overall measure of the effect of the one toxicant compared to another. In terms of the quality assessment of the non-randomized studies, only one reviewer assessed the quality of those studies and completed the required checklists. Lastly, although the Downs and Black (1997) quality assessment checklist was deemed suitable to use to assess the quality of the cross-sectional studies, this tool is somewhat outdated, and the use of a more recent assessment tool could have been more appropriate based on the prevalence of the fairly recent studies included in the review.

While this review did exhibit some limitations, there were also some important strengths. This review was able to consider a variety of environmental toxicants as part of the search criteria in the investigation of risk factors for the development of postpartum depression and did

not exclusively focus on more conventional toxicants (i.e. pesticides, cigarette smoke). This review included worldwide studies as part of the article selection process and was therefore not limited to North American studies. Throughout the article screening process (i.e. screening articles based on title and abstract, and then full-text screening) there was a second reviewer (undergraduate student) who performed the same process and therefore made it possible to discuss and observe any inconsistencies in selecting the relevant articles. Furthermore, the same reviewer also contributed to the quality assessment of the randomized-controlled trials in the review by utilizing the Cochrane Risk of Bias Tool and therefore made it possible to discuss and observe any inconsistencies as well.

**VII) Conclusion**

The findings from this review demonstrate the current knowledge and understanding surrounding the topic of environmental toxicants as risk factors for postpartum depression. Based on the results from the included studies, the literature does support a link between certain categories of environmental toxicants and the development of postpartum depression – majority involving cigarette/tobacco smoke exposure and some evidence regarding particulate air matter exposure – although, there are other studies in this review which found inconclusive and/or differing results. Given these variations, this systematic review could present as a foundation for encouraging future research to investigate this matter, in order to attain a greater perspective when conducting further studies. Additionally, there seems to be existing policies and regulations set in place by the Government of Canada regarding the environment and its effect on human health, as well as accessible and informative services and resources regarding mental health and the Canadian population, however, there is an absence of recognition surrounding the apparent interconnection between the two.

We are constantly exposed to a variety of environmental toxicants and substances, often without awareness to the extent of this exposure, with a great potential to profoundly impact our health. A better knowledge of a potential role for certain environmental toxicants on the onset and progression of mood disorders such as postpartum depression could influence its diagnosis and treatment with important consequences for the mother, child, and family.

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# Appendix I: Figures

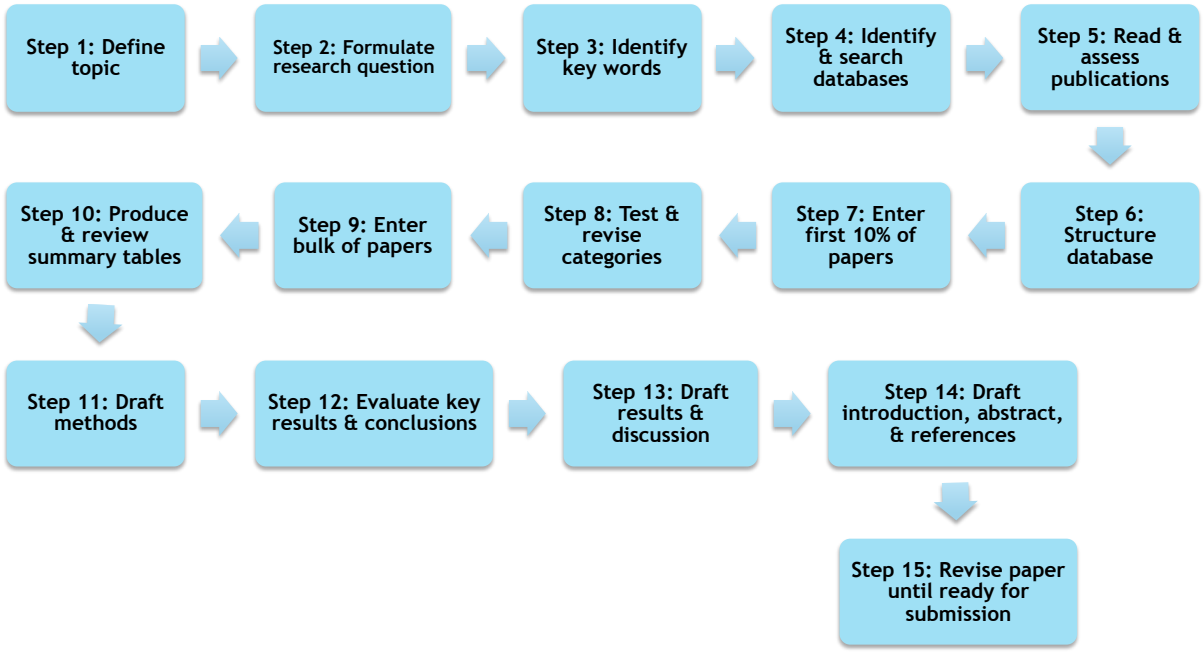


*Figure 1.* Steps in a systematic review. This figure outlines the required steps for conducting a systematic review as suggested by Pickering and Byrne (2013). The green checkmarks highlight the steps already completed, while the rest are those which have yet to be finalized.

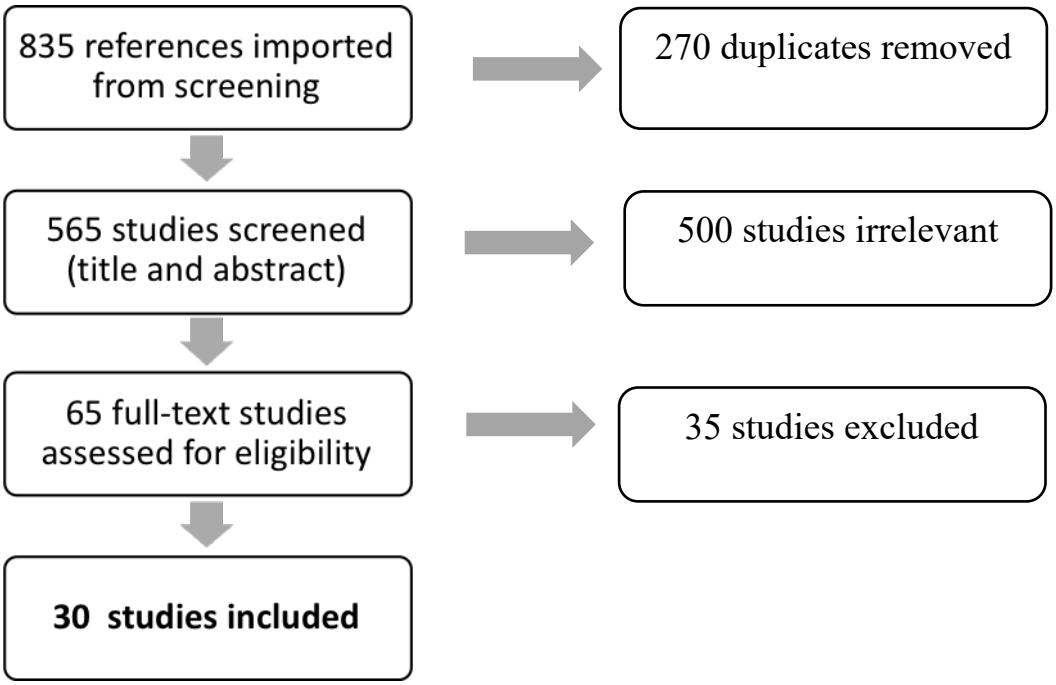


*Figure 2.* PRISMA Flow chart. This figure represents the selection process for identifying relevant articles to include in the systematic review. Formatted on: Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org

# Appendix II: Tables

*Table 1. Personal database for all included studies (n=30).*

| Author(s) & Year of Publication | Population | Aim of Study | Study Design | Interventions | Primary Outcomes |
|---|---|---|---|---|---|
| Alibekova et al. (2016) | 533 participants (pregnant women and their husbands); | Examine the effects of active and passive smoking on maternal depression | Prospective Cohort | Passive smoking (SHS) | Paternal smoking in the mother's presence (SHS) was associated with a significant increase in maternal perinatal depression compared with a non-smoking status |
| Chen et al. (2018) | 13 studies with 1,476,922 women | Examine the relationship between prenatal smoking and PPD | Systematic Review: Meta-analysis | Prenatal active smoking | Prenatal smoking was associated with PPD |
| Coletta et al. (2010) | N/A | Discuss the benefits of omega-3 fatty acid consumption during pregnancy | Literature Review | Omega-3 Fatty Acid intake | Reduces risk of depression in the postpartum period |
| Dagher and Shenassa (2012) | 526 women (8-weeks postpartum) | Investigate the associations of cigarette smoking, caffeine intake, vitamin intake, during pregnancy with postpartum depression | Prospective Cohort | Prenatal active smoking, and caffeine and vitamin intake | Prenatal smoking was associated with worse depressive symptoms at 8-weeks postpartum |
| Derbyshire and Costarelli (2008) | N/A | Discuss the main dietary factors implicated in the aetiology and treatment of PND | Literature Review | Omega-3 fatty acids, folate, B vitamins, calcium, zinc, and magnesium | Riboflavin, zinc, and calcium might have played a role in alleviating symptoms of PND; *n*-3 intake and PND incidence findings are contradictory |

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| Ellsworth-Bowers and Corwin (2012) | N/A | Review evidence for a link between micronutrient status and PPD | Literature Review | *n*-3 PUFA, B vitamins, vitamin D, zinc, and selenium | Varying results; primarily found a link between vitamin $B_{12}$ and PPD |
| Fard et al. (2017) | 99 women; 48 hours postpartum | Determine the effects of zinc and magnesium supplements on depressive symptoms in postpartum women | Randomized controlled Trial; triple blind | Zing and Magnesium Supplements | No significant difference was found; neither supplements reduced depressive symptoms |
| Frandsen et al. (2017) | 14,300 women | Investigate the demographic and smoking characteristics of pregnant women who smoked and were able to quit | Population-based cohort study (longitudinal) | Active smoking; intake of other substances (alcohol, drugs) | Smoking during pregnancy increased the risk of developing PPD; women who quit were less likely to develop PPD |
| Freeman (2006) | N/A | Determine what is currently known about omega-3 fatty acids and perinatal depression | Literature Review | Omega-3 Fatty Acids (EPA and DHA) | All participants whom received EPA and DHA doses, decreased mean EPDS scores by 52% |
| Glenville (2006) | N/A | Examine whether nutritional supplements during pregnancy play a role in the health of the mother | Literature Review | Nutritional Supplements (omega-3 fatty acids; seafood consumption) | Omega-3 fatty acid doses showed significant changes in depression scores postpartum |
| Hantsoo et al. (2014) | 38 women; postpartum depression onset within 3 months of delivery | Compare sertraline to placebo for treating PMD* | Randomized control trial; double-blind | Sertraline (SSRI) | Sertraline produced a significantly greater response rate (59%) than placebo (26%) and a more than 2-fold increased remission rate (53% vs. 21%) |
| Howard et al. (2005) | Two trials involving a total | Compare the effectiveness of | Intervention Review | Antidepressants (sertraline and | Nortriptyline did not show any benefit over placebo; |

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| | of 73 participants (women) | different antidepressant drugs and assess any adverse effects | | nortriptyline) | sertraline reduced the recurrence of postnatal depression compared with placebo |
| Kalayasiri et al. (2018) | 106 postpartum women | Study the effects of exposure to SHS on the QOL of pregnant and postpartum women | Cross-sectional | Second-hand smoke exposure | SHS was not associated with PPD |
| Khan et al. (2015) | 6884 women (2004-2008 North Carolina PRAMS Survey) | Explore the relationship between prenatal exposure to SHS during pregnancy and PPDS | Longitudinal (2004-2008 North Carolina PRAMS Survey) | Second-hand smoke exposure | SHS exposure was associated with almost twice the odds of PPDS |
| Leung and Kaplan (2009) | N/A | Examine the role of nutrition in perinatal depression | Literature Review | n-3 fatty acids, vitamin B12, calcium, iron, and zinc | High levels of DHA (omega-3 fatty acid) were positively predictive of lower rates of PPD; low intake of these nutrients, associated with an increased risk |
| Mbah et al. (2013) | 236 pregnant women | Determine the impact of passive smoking on the risk for depressive symptoms during pregnancy | Prospective Cohort | Environmental/passive smoke exposure | Those exposed to ETS were at an elevated risk for antenatal depressive symptoms |
| Molyneaux et al. (2018) | Two trials including a total of 81 participants | Assess the effectiveness of antidepressant medication for the prevention of postnatal depression | Intervention Review | Antidepressants (sertraline and nortriptyline) | Sertraline was more effective than placebo in preventing postnatal depression; nortriptyline was not more effective than placebo |
| Munafò et al. (2008) | 7,089 women | Determine whether smoking cessation during and immediately | Prospective Cohort | Active smoking/smoking status | Abstinence trajectory demonstrated the lowest amount of depression scores; |

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| | | following pregnancy is associated with changes in depression symptoms | | | persistent smokers had an increased in depression scores (postnatal) |
| Pariser et al. (1997) | N/A | N/A | Literature Review | Antidepressants | Antidepressant use in pregnancy was found to decrease the risk of developing PPD |
| Salimi et al. (2015) | 29,654 women (2004-2008 PRAMS Survey) | Examine the relationship between PPD and the changes in cigarette smoking behaviour across 3 time points | Longitudinal (2004-2008 PRAMS Survey) | Active smoking | Women who smoked prior to pregnancy and continued to smoke during the last 3 months of pregnancy and postpartum were more likely to have PPD compared to women who quit |
| Sheffield et al. (2018) | 598 women | Study the link between ambient air pollution exposure with psychological disfunction among postpartum women | Prospective Cohort | Particulate air pollution exposure | In race stratified analyses, increased $PM_{2.5}$ exposure (mid-pregnancy) was significantly associated with higher total postpartum EPDS scores |
| Singata-Madliki et al. (2016) | 242 postpartum women | Determine whether DMPA increases the risk of PND compared with the copper containing IUD when administered after delivery | Randomized controlled trial; single-blind | Oral contraceptive (DMPA) | One-month EPDS depression scores were statistically significantly higher in the DMPA arm compared with the IUD arm |
| Song et al. (2018) | 8,842 women | N/A | Prospective cohort | Active and passive smoking | Passive exposure to smoke was associated with PPD |
| Sparling et al. (2017) | N/A | Synthesize the evidence on whether dietary intake influences the risk of depression in the | Systematic review | Vitamins B & D, calcium, zinc, fish intake, PUFAs | Limited evidence was found regarding the influence of dietary intake on the risk of perinatal depression |

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| | | perinatal period | | | |
| Sunder et al. (2004) | 11 women | Differentiate characteristics of a discontinuation syndrome from a recurrence of PMDD in the context of a randomized trial | Randomized controlled trial; double-blind | Antidepressant (sertraline) | No significant difference was found between sertraline and placebo |
| Underwood et al. (2017) | 5,301 women | Explore whether risk factors differ for depression symptoms that are present during pregnancy and/or after childbirth | Longitudinal cohort | Variety of risk factors (of which, being prenatal active smoking and alcohol consumption) | Prenatal active smoking and alcohol consumption was not found to be significantly associated with PDS at 9 months after childbirth; |
| Vivilaki et al. (2016) | 300 women | Explore the perceptions, attitudes, and behaviours towards active and passive maternal smoking during pregnancy of smokers, non-smokers, and quitters | Cross-sectional survey | Active and passive smoking | Pregnant smokers (active) had significantly higher levels of postnatal depressive symptomatology, than non-smokers |
| Wang et al. (2018) | 973 women | Investigate the association between THS exposure during pregnancy and PPD | Cross-sectional | Third-hand smoke exposure | Compared with those who were never exposed to THS were at a higher risk of PPD |
| Weng et al. (2016) | 3,867 women | Investigate the relationships of smoking/second-hand smoke exposure status with depression from the first trimester to the first month postpartum | Cross-sectional | Active and passive smoke exposure (SHS) | Second-hand smoke exposure was positively associated with perinatal depression; those exposed had an increased risk of perinatal depression |

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| Yalçin et al. (2015) | 75 postpartum women | Evaluate the relation between OCPs and maternal psychopathologies | Cross-sectional | Organochlorine pesticides | No relation was detected between OCPs and EPDS at 8 months postpartum |

SHS: second-hand smoke
PPD: postpartum depression
*PMD: authors referred to it as postpartum depression
PND: postnatal depression
EPA: eicosapentaenoic acid
DHA: docosahexaenoic acid
IUD: intrauterine device
SSRI: selective serotonin reuptake inhibitor
PPDS: postpartum depression symptoms
ETS: environmental tobacco smoke
$PM_{2.5:}$ particulate matter (with an aerodynamic diameter 2.5 μm)
DMPA: depot medroxyprogesterone acetate
PUFA: polyunsaturated fatty acids
PMDD: postpartum major depressive disorder
THS: third-hand smoke
OCP: organochlorine pesticide

*Table 2. Summary table listing the percentage of articles in the different categories. Categories include: study designs and interventions among the articles (n=30)*

| **Study Design** | **Number of Articles (%)**<br>% = n/30 x 100 |
|---|---|
| **Literature Reviews**<br>(including systematic and intervention) | 37% |
| **Cohort Studies** | 33% |
| **Cross-sectional Studies** | 17% |
| **Randomized Controlled Trials** | 13% |
| **Interventions**<br>**(Environmental Toxicants)** | **Number of Articles (%)**<br>% = n/30 x 100 |
| **Smoke Exposure**<br>Active and passive (SHS) | 47% |
| **Dietary Supplements**<br>Micronutrients, omega-3 fatty acids | 27% |
| **Antidepressants**<br>Sertraline, nortriptyline | 17% |
| **Air Pollution**<br>Particulate air pollution | 3% |
| **Oral Contraceptives**<br>Depot medroxyprogesterone acetate (DMPA) | 3% |
| **Pesticides**<br>Organochlorine pesticides | 3% |

*Table 3. Data extraction table pertaining to study characteristics of the included studies (n=30)*

| Author & Year of Publication | Study Design | Location | Participants | Interventions and Comparators | Study Outcomes | Analyses | Length of follow up |
|---|---|---|---|---|---|---|---|
| Alibekova et al. (2016) | Prospective Cohort | Taipei, Taiwan | 1066 participants (pregnant women and their husbands); 509 women | Passive smoking (SHS) | Paternal smoking in the mother's presence (SHS) was associated with a significant increase in maternal perinatal depression compared with a non-smoking status | Descriptive statistics were employed to summarize he demographic characteristics of the sample (categorical variables described as percentages; continuous data presented as mean and standard deviation (SD)). Generalized estimating equation (GEE) analysis was conducted to estimate the longitudinal link between second-hand smoke status and parental depressive symptoms across perinatal periods. | 6 months postpartum |
| Chen et al. (2018) | Systematic Review: Meta-analysis | (China) of the 13 studies, 5 were conducted in USA, 2 in Canada, and the rest of 6 conducted in Finland, UK, Chile, Greece, Sweden and Turkey. | 13 studies with 1,476,922 women | Prenatal active smoking | Prenatal smoking was associated with PPD | The summary OR was calculated by pooled ORs and their 95% CI. Overall effects were determined using Z-test. Statistical heterogeneity was explored by inconsistency (I2) statistic; an I2 value of 50% or more represented substantial heterogeneity. Studies were pooled using a random-effects model if there was significant heterogeneity or fixed-effect model if no heterogeneity was observed. | -- |
| Coletta et al. (2010) | Literature Review | N/A | N/A | Omega-3 Fatty Acid intake | Reduces risk of depression in the postpartum period | N/A | -- |
| Dagher and Shenassa (2012) | Prospective Cohort | Mid-size northeastern city in the United States | 526 women | Prenatal active smoking, and caffeine and vitamin intake | Prenatal smoking was associated with worse depressive symptoms at 8-weeks postpartum | Hierarchical regression analysis | 8-weeks postpartum |

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|---|---|---|---|---|---|---|---|
| Derbyshire and Costarelli (2008) | Literature Review | N/A | N/A | Omega-3 fatty acids, folate, B vitamins, calcium, zinc, and magnesium | Riboflavin, zinc, and calcium might have played a role in alleviating symptoms of PND; n-3 intake and PND incidence findings are contradictory | N/A | -- |
| Ellsworth-Bowers and Corwin (2012) | Literature Review | N/A | N/A | *n-3 PUFA, B vitamins, vitamin D, zinc, and selenium* | Varying results; primarily found a link between vitamin B12 and PPD | N/A | -- |
| Fard et al. (2017) | Randomized controlled Trial; triple blind | Tabriz, Iran | 99 women | Zing and Magnesium Supplements | No significant difference was found; neither supplements reduced depressive symptoms | The chi-square, chi-square test for trend, Fisher's exact, and One-way ANOVA tests were used to compare the groups on socio-demographic characteristics.<br>One-way ANOVA was used to compare the mean scores of depressive symptoms before the intervention, and ANCOVA was used to compare depressive symptoms after 8-weeks of receiving the intervention. | -- |
| Frandsen et al. (2017) | Population-based cohort study (longitudinal) | Tasmania, Australia | 14,300 women | Active smoking; intake of other substances (alcohol, drugs) | Smoking during pregnancy increased the risk of developing PPD; women who quit were less likely to develop PPD | Mean (SE) to compare maternal smokers who quit in second half of pregnancy compared to those who did not.<br>Independent sample t-tests and Pearson's chi-square test to determine difference between the two population means. | N/A |
| Freeman (2006) | Literature Review | N/A | N/A | Omega-3 Fatty Acids (EPA and DHA) | All participants whom received EPA and DHA doses, decreased mean EPDS scores by 52% | N/A | -- |
| Glenville (2006) | Literature Review | N/A | N/A | Nutritional Supplements (omega-3 fatty acids; seafood consumption) | Omega-3 fatty acid doses showed significant changes in depression scores postpartum | N/A | -- |

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|---|---|---|---|---|---|---|---|
| Hantsoo et al. (2014) | Randomized control trial; double-blind | Greater New Haven and southern Connecticut areas (United Sates) | 36 women | Sertraline (SSRI) | Sertraline produced a significantly greater response rate (59%) than placebo (26%) and a more than 2-fold increased remission rate (53% vs. 21%) | Continuous variables were compared using two-sided t-tests, while categorical variables were compared using X2 tests when expected cell couts were greater than 5 or Fisher's exact tests (FET) otherwise. | -- |
| Howard et al. (2005) | Intervention Review | N/A | Two trials involving a total of 73 women | Antidepressants (sertraline and nortriptyline) | Nortriptyline did not show any benefit over placebo; sertraline reduced the recurrence of postnatal depression compared with placebo | The relative risk and 95% CIs were calculated for results using categorical data. Continuous data were pooled as weighted mean differences.<br>When overall results were significant, the NNT to prevent one woman developing PND was calculated. | -- |
| Kalayasiri et al. (2018) | Cross-sectional | Bangkok, Thailand | 106 women | Second-hand smoke exposure | SHS was not associated with PPD in their cohort | Descriptive statistics for demographics, exposure to SHS, and mental health were analyzed in PW and PPW groups. Demographics, SHS exposure status, and postpartum depression were compared between women with high and low to moderate levels of QOL in the two cohorts by using Chi-square or Fisher's exact test. | -- |
| Khan et al. (2015) | Longitudinal Cohort | North Carolina, United States | 6884 women (2004-2008 North Carolina PRAMS Survey) | Second-hand smoke exposure | SHS exposure was associated with almost twice the odds of PPDS | Descriptive statistics were used to examine the sample characteristics and to estimate the prevalence of SHS and PPDS. Unadjusted and adjusted odds ratios and 96% CIs were calculated using univariable and multivariable logistic regression analyses. | 2-6 months postpartum |
| Leung and Kaplan (2009) | Literature Review | N/A | N/A | n-3 fatty acids, vitamin B12, calcium, iron, and zinc | High levels of DHA (n-3 fatty acid) were positively predictive of lower rates of PPD; low intake of these nutrients, associated with an increased risk | N/A | -- |

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| Mbah et al. (2013) | Prospective Cohort | Tampa, Florida (United States) | 236 women | Environmental/passive smoke exposure | Those exposed to ETS were at an elevated risk for antenatal depressive symptoms | Latent variable modelling | 6-weeks postpartum |
| Molyneaux et al. (2018) | Intervention Review | N/A | Two trials including a total of 81 participants | Antidepressants (sertraline and nortriptyline) | Sertraline was more effective than placebo in preventing postnatal depression; nortriptyline was not more effective than placebo | The authors presented the primary outcome (postpartum depression) using risk ratios (RR) for all studies.<br>The authors calculated the RR and its 95% CI for dichotomous outcome data.<br>The authors did not conduct a meta-analysis for this review. | -- |
| Munafò et al. (2008) | Prospective Cohort | Southwest United Kingdom | 7,089 women | Active smoking/smoking status | Abstinence trajectory demonstrated the lowest amount of depression scores; persistent smokers had an increased in depression scores (postnatal) | Longitudinal latent class analysis (LLCA) models were defined and estimated with the Mplus framework (Muthén & Muthén, 1998-2006). | -- |
| Pariser et al. (1997) | Literature Review | N/A | N/A | Antidepressants | Antidepressant use in pregnancy was found to decrease the risk of developing PPD | N/A | -- |
| Salimi et al. (2015) | Longitudinal Cohort | PRAMS data was collected from 23 states and New York City (United States) | 29,654 women (2004-2008 PRAMS Survey) | Active smoking | Women who smoked prior to pregnancy and continued to smoke during the last 3 months of pregnancy and postpartum were more likely to have PPD compared to women who quit | Population proportions were reported with 95% CIs. The weighted univariate analysis applying Chi square testing was performed to evaluate the assocaiont of the individual independent variables or confounders with PPD using p=0.05 as level of significance. Weighted univariate and multivariate logistic analyses were performed reporting crude and adjusted OR. Effect sizes for the ORs of the association between PPD and perinatal smoking were calculated using the standard formula. | 2-9 months postpartum |

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|---|---|---|---|---|---|---|---|
| Sheffield et al. (2018) | Prospective Cohort | Boston, Massachusetts (United States) | 598 women | Particulate air pollution exposure | In race stratified analyses, increased PM2.5 exposure (mid-pregnancy) was significantly associated with higher total postpartum EPDS scores | Distributed lag models (DLMs) were used to estimate the time-varying association between weekly estimated PM2.5 level during pregnancy and the postpartum psychological outcomes.<br>To examine race-specific associations, DLMs stratified by race/ethnicity were also conducted. | 6 and 12 months postpartum |
| Singata-Madliki et al. (2016) | Randomized controlled trial; single-blind | East London, South Africa | 242 women | Oral contraceptive (DMPA) | One-month EPDS depression scores were statistically significantly higher in the DMPA arm compared with the IUD arm | Depression was analyzed as both a categorical and continuous variable. Categorical outcomes were compared between study groups using Chi-square (X2) test, or Fisher's exact two-tailed test. T-tests were used to compare means and SDs for normally distributed continuous data. Wilcoxon test was used to compare medians and interquartile ranges for non-parametric data. | -- |
| Song et al. (2018) | Prospective cohort | Tianjin, China | 8,842 women | Active and passive smoking | Passive exposure to smoke was associated with PPD | Continuous variables were expressed as means ± SDs, median ± interquartile range, and categorical variables were expressed by frequencies and percentages. Differences between the cohorts were tested using Student's t-test or a two-sample Mann-Whitney U-test for categorical variables. ORs and 95% CIs of smoking status for PPD were obtained using binary logistic regression in univariate and multivariate analyses. | 1-4 weeks postpartum |
| Sparling et al. (2017) | Systematic review | N/A | N/A | Vitamins B & D, calcium, zinc, fish intake, PUFAs | Limited evidence was found regarding the influence of dietary intake on the risk of perinatal depression | Study characteristics and overall results were extracted from all inlcuded studies using a standard data form. Meta-analysis was not possible. A descriptive summary of all included studies. | -- |

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|---|---|---|---|---|---|---|---|
| Sunder et al. (2004) | Randomized controlled trial; double-blind | N/A | 11 women | Antidepressant (sertraline) | No significant difference was found between sertraline and placebo | Categorical outcomes were compared between study groups using Chi-square ($X2$) test | -- |
| Underwood et al. (2017) | Longitudinal cohort | New Zealand | 5,301 women | Variety of risk factors (of which, being prenatal active smoking and alcohol consumption) | Prenatal active smoking and alcohol consumption was not found to be significantly associated with PDS at 9 months after childbirth; | Chi-square/*t* test analyses were used to determine univariable associations between ADS/PDS and categorical/continuous variables.<br>Only factors associated with depression status at $p<0.01$ at univariate level were included in the multinomial and binary logistic refression analyses. | 9 months postpartum |
| Vivilaki et al. (2016) | Cross-sectional survey | Athens, Greece | 300 women | Active and passive smoking | Pregnant smokers (active) had significantly higher levels of postnatal depressive symptomatology, than non-smokers | *T*-tests were carried out to compare the descriptive variables, risk perception, atitudes to smoking, smoking behaviours of women who smoked during pregnancy. Reliability coefficients, as measured by Cronbach's alpha, were calculated for the smoking questionnaire. | -- |
| Wang et al. (2018) | Cross-sectional | Shandong Province, China | 973 women | Third-hand smoke exposure | Compared with those who were never exposed to passive smoking, puerperal women who were exposed to THS were at higher risk of PPD. | Continuous variables were summarized as mean ± SD. Student t-tests were used to examined differences in means for conitnuous variables among participants were PPD and those without PPD. Categorical variables were presented as proportion (%) and compared using Chi-squared tests. Logistic regressino analyses were performed to estimate ORs and 95% CIs of the association between different forms of THS and risk of PPD. | -- |

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| Weng et al. (2016) | Cross-sectional | Taipei, Taiwan | 3,867 women | Active and passive smoke exposure (SHS) | Second-hand smoke exposure was positively associated with perinatal depression; those exposed had an increased risk of perinatal depression | Univariate and multivariate logistic regression models were used for analysis. Multivariate regression models with ORs and 95% CIs. | -- |
| Yalçin et al. (2015) | Cross-sectional | Ankara, Turkey | 75 women | Organochlorine pesticides | No relation was detected between OCPs and EPDS at 8 months postpartum | For comparing proportions, chi-square or Fisher's exact test was used when applicable. The correlations were examined using Spearman's rank order correlation coefficient. | -- |

*Table 4. Data extraction table pertaining to participant characteristics of the included studies.*

| **Author & Year of Publication** | **Participants' characteristics (sex, age, ethnicity; other specific characteristics if mentioned)** |
|---|---|
| Alibekova et al. (2016) | Female and male participants (males represent SHS exposure). Female participants: <30 years (11.2%), 30-35 (59.7%), >35 (29.1%). The participants were recruited in Taiwan however no further information pertaining to ethnicity was provided. |
| Chen et al. (2018) | *Meta-analysis* - 13 studies with 1,476,922 women that met the inclusion criteria for meta-analysis. Of the 13 studies, 5 were con-ducted in USA, 2 in Canada, and the rest of 6 con- ducted in Finland, UK, Chile, Greece, Sweden and Turkey. |
| Coletta et al. (2010) | *Literature Review* - N/A |
| Dagher and Shenassa (2012) | Female participants. The mean age was 28 years old. 76% were Caucasian. |
| Derbyshire and Costarelli (2008) | *Literature Review* - N/A |
| Ellsworth-Bowers and Corwin (2012) | *Literature Review* - N/A |
| Fard et al. (2017) | Female participants. The mean ages (standard deviations) in the zinc sulfate, magnesium sulfate, and control groups were 29.4 (5.4), 26.4 (4.8), and 27.6 (5.1) years, respectively. No statistically significant differences were observed in socio-demographic and obstetric characteristics among the three groups. The participants were living in Tabriz, but no further information pertaining to ethnicity was mentioned. |
| Frandsen et al. (2017) | The mean age was 28.16 years old, 90.3% were born in Australia and 5.9% were Indigenous. Females |
| Freeman (2006) | *Literature Review* - N/A |
| Glenville (2006) | *Literature Review* - N/A |

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|---|---|
| Hantsoo et al. (2014) | Female participants. Mean±SD age of participants was 30.8±4.0 years, with no between-group (sertraline vs placebo) differences in demographic variables. Likewise, treatment groups were similar with respect to timing of onset of MDD, duration of illness and the number of weeks post-childbirth at the time of enrollment. Women were included only if they were English-speaking and they were recruited from the greater New Haven and southern Connecticut area, but not further information regarding ethnicity was mentioned. |
| Howard et al. (2005) | *Intervention Review* - N/A |
| Kalayasiri et al. (2018) | Female participants. The mean age was 31 years old. Participants were recruited from Bangkok, Thailand but no further information regarding ethnicity was mentioned. |
| Khan et al. (2015) | Female participants. The researchers controlled for age of participants as a potential confounder, however no specific mention of the ages of participants was provided. The majority of the participants identified themselves as Caucasians (73.3%), followed by African-American (22.3%). Other races including Hispanics, Asians and Native Americans constituted 4% of the total participants. |
| Leung and Kaplan (2009) | *Literature Review* - N/A |
| Mbah et al. (2013) | Non-smokers (15 were <30 years, 8 were >30 years); Passive smokers (85 were <30 years, 21 were >30 years), Smokers (88 were <30 years, 19 were >30 years). Close to 77% of participants were African-American or Hispanics. Females. |
| Molyneaux et al. (2018) | *Intervention Review* - N/A |
| Munafò et al. (2008) | Female participants. The mean age at birth of the final included sample (n=57,089) was 29 years. Participants were recruited in the United Kingdom however no further information pertaining to ethnicity was provided. |
| Pariser et al. (1997) | *Literature Review* - N/A |
| Salimi et al. (2015) | Female participants. 23% were >30 years, 29% were 25-29 years, 35% were 20-24 years, and 13% were <20 years. 79% were Caucasian/non-Hispanic, 10% were African-American/non-Hispanic, 5% were Hispanic, and 6% were Other/non-Hispanic. |

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|---|---|
| Sheffield et al. (2018) | Female participants. The mean age was 25.8 years. They were primarily Hispanic (55%) and African-American (29%). |
| Singata-Madliki et al. (2016) | Female participants. The median age was 26 years. The participants were recruited in two hospitals in South Africa, who serve a mainly Black, Xhosa-speaking, South African population. No further information regarding ethnicity was provided. |
| Song et al. (2018) | Female participants. The mean age was 28.5 years. The participants were recruited in China however no further information pertaining to ethnicity was provided. |
| Sparling et al. (2017) | *Systematic Review* - N/A |
| Sunder et al. (2004) | Female participants. The mean age was 32 years. The location of the study was not provided, therefore there is no information pertaining to ethnicity of participants. |
| Underwood et al. (2017) | Female participants. The mean age was 30 years old. 56% were European, 13.2% were Māori, 12.8% were Pacific, 14.2% were Asian, and 3.8% were Other. |
| Vivilaki et al. (2016) | Female participants. The mean age was 33.76 years. Nationality of participants was provided: 85% were Greek and 15% were Other. No further information pertaining to ethnicity was provided. |
| Wang et al. (2018) | Female participants. The mean age was 28.6 ± 5.44 years. Participants were recruited from the east of China however no further information pertaining to ethnicity was provided. |
| Weng et al. (2016) | Female participants. 4.47% were ≤ 25 years, 73.93% were 26-35 years and 21.59% were ≥ 36 years. The participants were recruited in Taiwan and they excluded from the study if they could not read or write Chinese, however no further information pertaining to ethnicity was provided. |
| Yalçin et al. (2015) | Female participants. 17 were <20 years, and 58 were ≥ 20 years. Participants were recruited in Turkey, however no further information pertaining to ethnicity was provided. |

*Table 5. Risk of bias entry for a randomized controlled trial included in the systematic review. Fard et al. (2017)*

| Entry | Judgment | Support for judgment |
|---|---|---|
| Selection bias | Low risk | Quote: "the method of sampling was purposeful, and the criteria used to identify and select participants were women aged 18+ years old, given birth in the last 48 hours and living in Tabriz."; 99/187 women participated in the study (52%); participants from 3 different hospitals in Tabriz<br>Comment: representative of target population |
| Allocation bias | Low risk | Quote: "the eligible participants were assigned to one of three groups (two intervention groups and one control group) by blocked randomization with block sizes of three and six and an allocation ratio of 1:1:1:" |
| Performance Bias | Low risk | Quote: "…medications were placed inside sealed and sequentially numbered envelopes. The envelopes were prepared based on the allocation sequence by a person uninvolved in the research. Masking of researcher and participants were maintained." |
| Detection Bias | Low risk | Quotes: "Those involved in sampling and data collection, analyzers, and participants were unaware of the type of intervention received."; "triple-blind study" |
| Attrition bias | Low risk | Quote: "2 participants in the Zn sulfate group and 2 in the Mg sulfate group were excluded due to the lack of response and follow-up telephone calls."<br>Comment: equal rates between treatment groups; no attrition mentioned |
| Reporting bas | Low risk | Quote: "No significant differences were observed between the groups receiving zinc sulfate, magnesium sulfate, and the placebo group in terms of PPD symptoms."<br>Comment: All outcomes stated were reported. |

*Table 6. Risk of bias entry for a randomized controlled trial included in the systematic review. Hantsoo et al. (2014)*

| Entry | Judgment | Support for judgment |
|---|---|---|
| Selection bias | High risk | Quote: "A total of 17 women were randomized to the sertraline group and 19 were randomized to placebo, for a total of 36 women in the intent-to-treat group. Among those, 29 completed through week 7, 33 completed through week 4, and all 36 completed through week 2…"<br>Comment: Less than half ended up partaking in the study; not an equal distribution between two groups. |
| Allocation bias | Low risk | Quote: "A research pharmacist was responsible for creating a blinding table and distributing the study drug; all other study personnel remained blind to the subject treatment status."<br>Comment: Third party allocated the intervention, the study personnel remained blinded. |
| Performance Bias | Low risk | Quote: "Double blind placebo-controlled trail of sertraline with a one-week placebo lead-in." |
| Detection Bias | Low risk | Quotes: "Participants met weekly with a psychiatric nurse practitioner or masters-level psychologist to complete patient- and clinician-administered ratings and clinical assessment of symptoms and side effects for the duration of study."; "…blind to subject treatment status." |
| Attrition bias | High risk | Quote: "Reasons for failure to complete the full seven weeks included clinical deterioration (n=3, all in the placebo group), loss to follow-up (n=3), and accidental unblinding (n=1).<br>Comment: Majority in the placebo group and one accidental unblinding. |
| Reporting bas | Low risk | Quote: "The secondary analysis of responder status in women meeting strict DSM-IV criteria for PMD (onset of PMD within the first 4 weeks past giving birth) in the ITT sample (n=27) showed a significantly greater number of responders among those women randomized to sertraline (50%, 6/12) vs. those randomized to placebo (6.7%, 1/15)."<br>Comment: All results explained by summary tables. |

*Table 7. Risk of bias entry for a randomized controlled trial included in the systematic review. Singata-Madiliki et al. (2016)*

| Entry | Judgment | Support for judgment |
|---|---|---|
| Selection bias | Low risk | Quotes: "Those who expressed an interest in participating were referred to research mid-wives who determined their eligibility."; "Research midwives provided eligible women with further information about the trial and invited them to participate; those who were willing to participate signed the study information and consent form." |
| Allocation bias | Low risk | Quote: "A co-investigator not involved in recruitment or outcome assessment prepared a compute-generated random allocation sequence in balanced blocks of variable size in a ratio of 1:1." |
| Performance Bias | Low risk | Quote: "Allocation cards were packed and sealed in consecutively numbered, opaque envelopes by the data manager…" |
| Detection Bias | Low risk | Quote: "The principal investigator, who was not involved with screening or enrolment, performed telephone interviews. At enrolment, participants were requested to keep the contraception method confidential during subsequent telephonic follow-up to ensure that the interviewer remained blinded to the group allocation." |
| Attrition bias | Low risk | Quote: "Eight participants (three in the DMPA arm, five in the IUD arm) were excluded from analysis due to follow-up interviews, giving a total of 234 participants analyzed."<br>Comment: 234 participants analyzed (116 in the DMPA and 118 in the IUD – relatively equal distribution). |
| Reporting bas | Low risk | Quotes: "More women in the DMPA arm had severe depression at 1 and 3 months compared with the IUD according to the BDI-II scores (borderline statistical significance)."; "One-month depression scores were significantly higher with DMPA use compared with IUD use according to EPDS data; 3-month depression scores were higher with DMPA according to BDI-II data."<br>Comment: The outcomes for both groups were reported. |

*Table 8. Risk of bias entry for a randomized controlled trial included in the systematic review. Sunder et al. (2004)*

| Entry | Judgment | Support for judgment |
|---|---|---|
| Selection bias | High risk | Quote: "The mean age of subjects was 32 years (SD=3, range, 25-37). Women had had at least 1 prior episode of PMDD. Pregnant women who had recovered from this previous episode of depression were recruited."<br>Comment: Very little detail as to the methods used to recruit these participants. |
| Allocation bias | Unclear risk | Quote: "We administered sertraline or identical placebo through the first 17-weeks postpartum to cover the defined 3-month period of risk of PMDD recurrence."<br>Comment: No further mention as to how the interventions were allocated. |
| Performance Bias | Unclear risk | Quote: "The women were preventively medicated with sertraline or placebo immediately post-birth."<br>Comment: No indication if subjects were blinded when this happened. |
| Detection Bias | High risk | Quotes: "Drug assignment was known only to the study research pharmacist, the nonblinded medical monitor, and the study statistician. The medication monitoring function was separate from (and blinded to) the mood symptom monitoring."<br>Comment: Key personnel were not blinded to the allocation process. |
| Attrition bias | High risk | Quote: In the 14 women assigned to sertraline, 1 experienced recurrence at week 17, 4 withdrew, 1 was removed from the trial due to hypomania, and 8 completed the trial without recurrence. Therefore, 8 women who took sertraline and 3 women who took placebo entered the tapering phase (the focus of the report) of the original randomized trial."<br>Comment: Very little participants for a randomized-controlled trial. Unequal distribution of interventions, unequal number of attrition participants, and only 11 participants were considered for the main focus of this research project. |
| Reporting bas | Low risk | Quote: "At the end of each week of taper (weeks 18-20), low levels of symptoms from the ASE in both the sertraline- and placebo-treated groups were observed. There was no significant difference between sertraline- and placebo-treated women on the 9-item subset of the ASE."<br>Comment: The outcomes from both groups were reported. |

*Table 9. Summary of the quality assessments for the non-randomized studies included in the review.*

| Study (Author and Year) | Study Design | Quality Assessment Tool | Overall Quality |
|---|---|---|---|
| Alibekova et al. (2016) | Cohort | CASP Checklist | Satisfactory |
| Chen et al. (2018) | Literature Review | CASP Checklist | Good |
| Coletta et al. (2010) | Literature Review | CASP Checklist | Poor |
| Dagher and Shenassa (2012) | Cohort | CASP Checklist | Satisfactory |
| The Derbyshire and Costarelli (2008) | Literature Review | CASP Checklist | Satisfactory |
| Ellsworth-Bowers and Corwin (2012) | Literature Review | CASP Checklist | Satisfactory |
| Frandsen et al. (2017) | Cohort | CASP Checklist | Poor |
| Freeman (2006) | Literature Review | CASP Checklist | Poor |
| Glenville (2006) | Literature Review | CASP Checklist | Poor |
| Howard et al. (2005) | Literature Review | CASP Checklist | Satisfactory |
| Kalayasiri et al. (2018) | Cross-sectional | Downs and Black Checklist | Adequate |
| Khan et al. (2015) | Cohort | CASP Checklist | Satisfactory |

| | | | |
|---|---|---|---|
| Leung and Kaplan (2009) | Literature Review | CASP Checklist | Poor |
| Mbah et al. (2013) | Cohort | CASP Checklist | Adequate |
| Molyneaux et al. (2018) | Literature Review | CASP Checklist | Good |
| Munafò et al. (2008) | Cohort | CASP Checklist | Good |
| Pariser et al. (1997) | Literature Review | CASP Checklist | Poor |
| Salimi et al. (2015) | Cohort | CASP Checklist | Satisfactory |
| Sheffield et al. (2018) | Cohort | CASP Checklist | Poor |
| Song et al. (2018) | Cohort | CASP Checklist | Adequate |
| Sparling et al. (2017) | Literature Review | CASP Checklist | Good |
| Underwood et al. (2017) | Cohort | CASP Checklist | Adequate |
| Vivilaki et al. (2016) | Cross-sectional | Downs and Black Checklist | Good |
| Wang et al. (2018) | Cross-sectional | Downs and Black Checklist | Good |

| | | | |
|---|---|---|---|
| Weng et al. (2016) | Cross-sectional | Downs and Black Checklist | Good |
| Yalçin et al. (2015) | Cross-sectional | Downs and Black Checklist | Poor |

# Appendix III: Lists of Key Words

**Key Words used to search the database Medline (Ovid):**

| Search Entry | Query |
|---|---|
| 1. (sub-headings) | endocrine disruptors/ or environmental pollutants/ or aroclors/ or pentachlorophenol/ or polychlorinated biphenyls/ or polychlorinated dibenzodioxins/ or tetrachloroethylene/ or air pollutants/ or gasoline/ or hydrogen sulfide/ or particulate matter/ or sulfur dioxide/ or vehicle emissions/ or soil pollutants/ or heptachlor/ or water pollutants/ or water pollutants, chemical/- |
| 2. | endocrine disruptor*.ti,ab,kw.- |
| 3. | aroclor*.ti,ab,kw.- |
| 4. | pentachlorophenol.ti,ab,kw.- |
| 5. | polychlorinated biphenyl*.ti,ab,kw.- |
| 6. | pcb.ti,ab,kw.- |
| 7. | polychlorinated dibenzodioxin*.ti,ab,kw.- |
| 8. | tetrachloroethylene.ti,ab,kw.- |
| 9. | ((environment* or air or soil or water) adj3 (pollutant* or toxicant*)).ti,ab,kw.- |
| 10. | gasoline.ti,ab,kw.- |
| 11. | hydrogen sulfide.ti,ab,kw.- |
| 12. | particulate matter.ti,ab,kw.- |
| 13. | sulfur dioxide.ti,ab,kw.- |
| 14. | ((vehicle* or car? or automobile* or gas) adj2 (exhaust or emission*)).ti,ab,kw.- |
| 15. | heptachlor.ti,ab,kw.- |
| 16. | carbon dioxide/ or carbon monoxide/- |
| 17. | (carbon adj2 (monoxide or dioxide)).ti,ab,kw.- |
| 18. | Tobacco Smoke Pollution/- |
| 19. | (((second hand or passive) adj2 smok*) or ((tobacco or cigarette*) adj2 smok* adj2 pollution)).ti,ab,kw.- |
| 20. | metals, heavy/ or cadmium/ or copper/ or lead/ or mercury/ or zinc/- |
| 21. | ((metal* adj2 heavy) or cadmium or copper or lead or mercury or zinc).ti,ab,kw.- |
| 22. | pesticide*.ti,ab,kw.- |
| 23. | pesticides/ or pesticide residues/- |
| 24. | plasticizers/ or dibutyl phthalate/ or diethylhexyl phthalate/- |
| 25. | (plasticizer* or phthalate*).ti,ab,kw.- |
| 26. | bisphenol*.ti,ab,kw.- |
| 27. | persistent organic pollutant.ti,ab,kw.- |
| 28. | Volatile Organic Compounds/- |
| 29. | Volatile Organic Compound.ti,ab,kw.- |
| 30. | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29- |

| | |
|---|---|
| 31. | Depression, Postpartum/- |
| 32. | ((Puerperal or postnatal or perinatal) adj2 depress*).ti,ab,kw.- |
| 33. | ((Puerperal or postnatal or perinatal) adj2 mental health).ti,ab,kw.- |
| 34. | 31 or 32 or 33- |
| 35. | 30 and 34- |
| 36. | limit 35 to year="1995-Current year"- |

ti. = Search articles by title
ab. = Search articles by abstract
kw. = Search articles by keyword
ajd2 = Inclusion of terms in any order with 1-3 words between them
* = Inclusion of possible suffixes/plural form

**Key Words used to search the database CINAHL (Ebsco):**

| Search Entry | Query | # of Article Results |
|---|---|---|
| S48 | (S42 OR S43 OR S44 OR S45 OR S46) AND (S41 AND S47) | 118 |
| S47 | S42 OR S43 OR S44 OR S45 OR S46 | 4,124 |
| S46 | (MH "Depression, Postpartum") | 3,495 |
| S45 | TI "puerperal depression" OR AB "puerperal depression" | 7 |
| S44 | TI "perinatal depression" OR AB "perinatal depression" | 273 |
| S43 | TI "postpartum depression" OR AB "postpartum depression" | 1,391 |
| S42 | TI "postnatal depression" OR AB "postnatal depression" | 1,243 |
| S41 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 | 92,012 |
| S40 | (MH "Pesticides") OR (MH "Environmental Pollutants, Pesticides") | 2,101 |
| S39 | (MH "Metals, Heavy") OR (MH "Cadmium") OR (MH "Lead") OR (MH "Mercury") OR (MH "Copper") OR (MH "Zinc") | 6,082 |
| S38 | (MH "Passive Smoking") | 3,328 |
| S37 | (MH "Carbon Dioxide") | 3,055 |

| | | |
|---|---|---|
| S36 | (MH "Particulate Matter") | 1,535 |
| S35 | TI "volatile organic compounds" OR AB "volatile organic compounds" | 137 |
| S34 | TI bisphenol OR AB bisphenol | 374 |
| S33 | TI phthalates OR AB phthalates | 286 |
| S32 | TI "phthalic acid dibutyl ester" OR AB "phthalic acid dibutyl ester" | 0 |
| S31 | TI plasticizer OR AB plasticizer | 70 |
| S30 | TI pesticides OR AB pesticides | 1,915 |
| S29 | TI zinc OR AB zinc | 3,027 |
| S28 | TI copper OR AB copper | 1,379 |
| S27 | TI mercury OR AB mercury | 1,683 |
| S26 | TI lead OR AB lead | 66,216 |
| S25 | TI cadmium OR AB cadmium | 443 |
| S24 | TI "heavy metal" OR AB "heavy metal" | 262 |
| S23 | TI "tobacco smoking" OR AB "tobacco smoking" | 994 |
| S22 | TI "second hand smoking" OR AB "second hand smoking" | 17 |
| S21 | TI "passive smoking" OR AB "passive smoking" | 533 |
| S20 | TI "carbon monoxide" OR AB "carbon monoxide" | 1,947 |
| S19 | TI "carbon dioxide" OR AB "carbon dioxide" | 2,440 |
| S18 | TI "car emissions" OR AB "car emissions" | 0 |
| S17 | TI "gas emissions" OR AB "gas emissions" | 166 |
| S16 | TI "environmental pollutants" OR AB "environmental pollutants" | 139 |
| S15 | TI heptachlor OR AB heptachlor | 19 |
| S14 | TI "sulfur dioxide" OR AB "sulfur dioxide" | 155 |
| S13 | TI "particulate matter" OR AB "particulate matter" | 1,268 |
| S12 | TI "hydrogen sulfide" OR AB "hydrogen sulfide" | 180 |

| | | |
|---|---|---|
| S11 | TI gasoline OR AB gasoline | 267 |
| S10 | TI "tetrachloroethylene" OR AB "tetrachloroethylene" | 21 |
| S9 | TI "polychlorinated dibenzodioxin" OR AB "polychlorinated dibenzodioxin" | 1 |
| S8 | TI "polychlorinated biphenyl" OR AB "polychlorinated biphenyl" | 76 |
| S7 | TI "pentachlorophenol" OR AB "pentachlorophenol" | 13 |
| S6 | TI "water pollutants" | 0 |
| S5 | TI "persistent organic pollutants" OR AB "persistent organic pollutants" | 135 |
| S4 | (MH "Air Pollutants, Environmental") OR (MH "Air Pollutants, Occupational") OR (MH "Air Pollutants, Radioactive") OR (MH "Air Pollutants") | 2,124 |
| S3 | (MH "Carbon Monoxide") | 1,015 |
| S2 | TI aroclor* OR AB aroclor* | 19 |
| S1 | TI "endocrine disruptor*" OR AB "endocrine disruptor*" | 159 |

S# = search entry number
MH = Main Heading (a.k.a. Sub-heading)
TI = Search articles by title
AB = Search articles by abstract
* = Inclusion of plural for

**Key Words used to search the database EMBASE:**

| |
|---|
| 1. endocrine disruptor/ |
| 2. air pollutant/ or exhaust gas/ or smoke/ |
| 3. water pollutant/ or acid mine drainage/ or effluent/ or sewer outfall/ |
| 4. pollutant/ or persistent organic pollutant/ or soil pollutant/ |
| 5. aroclor/ |
| 6. pentachlorophenol/ |
| 7. polychlorinated biphenyl/ |
| 8. polychlorinated dibenzodioxin/ |
| 9. tetrachloroethylene/ |
| 10. gasoline/ |

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|---|
| 11. hydrogen sulfide/ |
| 12. particulate matter/ |
| 13. sulfur dioxide/ |
| 14. heptachlor/ |
| 15. endocrine disruptor*.ti,ab,kw. |
| 16. aroclor*.ti,ab,kw. |
| 17. pentachlorophenol.ti,ab,kw. |
| 18. polychlorinated biphenyl*.ti,ab,kw. |
| 19. pcb.ti,ab,kw. |
| 20. polychlorinated dibenzodioxin*.ti,ab,kw. |
| 21. tetrachloroethylene.ti,ab,kw. |
| 22. ((environment* or air or soil or water) adj3 (pollutant* or toxicant*)).ti,ab,kw. |
| 23. gasoline.ti,ab,kw. |
| 24. hydrogen sulfide.ti,ab,kw. |
| 25. particulate matter.ti,ab,kw. |
| 26. sulfur dioxide.ti,ab,kw. |
| 27. ((vehicle* or car? or automobile* or gas) adj2 (exhaust or emission*)).ti,ab,kw. |
| 28. heptachlor.ti,ab,kw. |
| 29. carbon dioxide/ |
| 30. carbon monoxide/ |
| 31. (carbon adj2 (monoxide or dioxide)).ti,ab,kw. |
| 32. passive smoking/ |
| 33. (((second hand or passive) adj2 smok*) or ((tobacco or cigarette*) adj2 smok* adj2 pollution)).ti,ab,kw. |
| 34. heavy metal/ or cadmium/ or lead/ or mercury/ |
| 35. ((metal* adj2 heavy) or cadmium or copper or lead or mercury or zinc).ti,ab,kw. |
| 36. pesticide*.ti,ab,kw. |
| 37. pesticide/ |
| 38. pesticide residue/ |
| 39. plasticizer/ |
| 40. phthalic acid dibutyl ester/ |
| 41. "phthalic acid bis(2 ethylhexyl) ester"/ |
| 42. (plasticizer* or phthalate*).ti,ab,kw. |
| 43. bisphenol*.ti,ab,kw. |
| 44. persistent organic pollutant.ti,ab,kw. |
| 45. persistent organic pollutant/ |
| 46. volatile organic compound/ |
| 47. Volatile Organic Compound.ti,ab,kw. |

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|---|
| 48. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 |
| 49. postnatal depression/ or perinatal depression/ |
| 50. ((Puerperal or postnatal or perinatal) adj2 depress*).ti,ab,kw. |
| 51. ((Puerperal or postnatal or perinatal) adj2 mental health).ti,ab,kw. |
| 52. 49 or 50 or 51 |
| 53. 48 and 52 |
| 54. limit 53 to yr="1995 -Current" |

ti. = Search articles by title
ab. = Search articles by abstract
kw. = Search articles by keyword
ajd2/3 = Inclusion of terms in any order with 2-3 words between them
* = Inclusion of possible suffixes/plural form
“” = Direct phrase

**Key Words used to search the database PsycINFO:**

| |
|---|
| 1. endocrine disruptor*.ti,ab. |
| 2. aroclor*.ti,ab. |
| 3. pentachlorophenol.ti,ab. |
| 4. polychlorinated biphenyl*.ti,ab. |
| 5. pcb.ti,ab. |
| 6. polychlorinated dibenzodioxin*.ti,ab. |
| 7. tetrachloroethylene.ti,ab. |
| 8. ((environment* or air or soil or water) adj3 (pollutant* or toxicant*)).ti,ab. |
| 9. gasoline.ti,ab. |
| 10. hydrogen sulfide.ti,ab. |
| 11. particulate matter.ti,ab. |
| 12. sulfur dioxide.ti,ab. |
| 13. ((vehicle* or car? or automobile* or gas) adj2 (exhaust or emission*)).ti,ab. |
| 14. heptachlor.ti,ab. |
| 15. carbon monoxide/ |
| 16. carbon dioxide/ |
| 17. (carbon adj2 (monoxide or dioxide)).ti,ab. |
| 18. passive smoking/ |
| 19. (((second hand or passive) adj2 smok*) or ((tobacco or cigarette*) adj2 smok* adj2 pollution)).ti,ab. |
| 20. ((metal* adj2 heavy) or cadmium or copper or lead or mercury or zinc).ti,ab. |
| 21. pesticide*.ti,ab. |

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| 22. insecticides/ |
| 23. (plasticizer* or phthalate*).ti,ab. |
| 24. bisphenol*.ti,ab. |
| 25. persistent organic pollutant.ti,ab. |
| 26. Volatile Organic Compound.ti,ab. |
| 27. postnatal depression/ |
| 28. ((puerperal or postnatal or perinatal or postpartum) adj2 depress*).ti,ab. |
| 29. ((puerperal or postnatal or perinatal) adj2 mental health).ti,ab. |
| 30. 27 or 28 or 29 |
| 31. Tobacco Smoking/ |
| 32. metallic elements/ or copper/ or "lead (metal)"/ or "mercury (metal)"/ or zinc/ |
| 33. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 31 or 32 |
| 34. 30 and 33 |
| 35. limit 34 to yr="1995 -Current" |

ti. = Search articles by title
ab. = Search articles by abstract
* = Inclusion of possible suffixes/plural form
ajd2 = Inclusion of terms in any order with 2 words between them
“” = Direct phrase

**Key Words used to search the database Toxline:**

| Search | Database | Query | Time | Result |
|---|---|---|---|---|
| # 36 | toxline | ( #30 AND #35 ) AND NOT PubMed [org] AND NOT pubdart [org] | 11:00:07 | 112 |
| # 35 | toxline | ( #31 OR #32 OR #33 OR #34 ) AND NOT PubMed [org] AND NOT pubdart [org] | 10:59:30 | 399 |
| # 34 | toxline | "maternal health" [not] PubMed [org] [not] pubdart [org] | 10:58:53 | 358 |
| # 33 | toxline | "perinatal depression" [not] PubMed [org] [not] pubdart [org] | 10:58:42 | 4 |
| # 32 | toxline | "postpartum depression" [not] PubMed [org] [not] pubdart [org] | 10:58:30 | 38 |
| # 31 | toxline | "postnatal depression" [not] PubMed [org] [not] pubdart [org] | 10:58:19 | 18 |
| # 30 | toxline | ( #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 ) AND NOT PubMed [org] AND NOT | 10:57:44 | 333695 |

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|---|---|---|---|---|
| | | pubdart [org] | | |
| # 29 | toxline | "volatile organic compound" [not] PubMed [org] [not] pubdart [org] | 10:56:38 | 5585 |
| # 28 | toxline | bisphenol [not] PubMed [org] [not] pubdart [org] | 10:56:28 | 1566 |
| # 27 | toxline | phthalate [not] PubMed [org] [not] pubdart [org] | 10:56:19 | 4693 |
| # 26 | toxline | plasticizer [not] PubMed [org] [not] pubdart [org] | 10:56:11 | 1816 |
| # 25 | toxline | pesticide [not] PubMed [org] [not] pubdart [org] | 10:56:02 | 118073 |
| # 24 | toxline | copper [not] PubMed [org] [not] pubdart [org] | 10:55:56 | 20626 |
| # 23 | toxline | mercury [not] PubMed [org] [not] pubdart [org] | 10:55:51 | 20548 |
| # 22 | toxline | lead [not] PubMed [org] [not] pubdart [org] | 10:55:40 | 101633 |
| # 21 | toxline | cadmium [not] PubMed [org] [not] pubdart [org] | 10:55:36 | 24268 |
| # 20 | toxline | "heavy metal" [not] PubMed [org] [not] pubdart [org] | 10:55:28 | 26920 |
| # 19 | toxline | "cigarette smoking" [not] PubMed [org] [not] pubdart [org] | 10:55:16 | 9525 |
| # 18 | toxline | "tobacco smoking" [not] PubMed [org] [not] pubdart [org] | 10:55:06 | 1545 |
| # 17 | toxline | "second hand smoking" [not] PubMed [org] [not] pubdart [org] | 10:54:51 | 7 |
| # 16 | toxline | "passive smoking" [not] PubMed [org] [not] pubdart [org] | 10:54:40 | 1291 |
| # 15 | toxline | "carbon monoxide" [not] PubMed [org] [not] pubdart [org] | 10:54:31 | 8044 |
| # 14 | toxline | "carbon dioxide" [not] PubMed [org] [not] pubdart [org] | 10:54:21 | 10143 |
| # 13 | toxline | "gas emission" [not] PubMed [org] [not] pubdart [org] | 10:54:10 | 1030 |
| # 12 | toxline | "vehicle emission" [not] PubMed [org] [not] pubdart [org] | 10:54:00 | 692 |
| # 11 | toxline | heptachlor [not] PubMed [org] [not] pubdart [org] | 10:53:50 | 2333 |
| # 10 | toxline | "sulfur dioxide" [not] PubMed [org] [not] pubdart [org] | 10:53:41 | 7091 |
| # 9 | toxline | "particulate matter" [not] PubMed [org] [not] pubdart [org] | 10:53:28 | 4949 |
| # 8 | toxline | "hydrogen sulfide" [not] PubMed [org] [not] pubdart [org] | 10:53:15 | 2548 |

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|---|---|---|---|---|
| # 7 | toxline | gasoline [not] PubMed [org] [not] pubdart [org] | 10:53:06 | 3470 |
| # 6 | toxline | tetrachloroethylene [not] PubMed [org] [not] pubdart [org] | 10:53:01 | 1626 |
| # 5 | toxline | "polychlorinated dibenzodioxin" [not] PubMed [org] [not] pubdart [org] | 10:52:53 | 499 |
| # 4 | toxline | "polychlorinated biphenyl" [not] PubMed [org] [not] pubdart [org] | 10:52:37 | 12862 |
| # 3 | toxline | pentachlorophenol [not] PubMed [org] [not] pubdart [org] | 10:52:24 | 2831 |
| # 2 | toxline | aroclor [not] PubMed [org] [not] pubdart [org] | 10:52:13 | 3799 |
| # 1 | toxline | "endocrine disruptor" [not] PubMed [org] [not] pubdart [org] | 10:52:03 | 1768 |

“” = Direct phrase