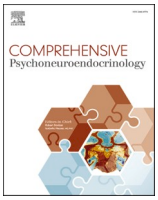
Comprehensive Psychoneuroendocrinology 16 (2023) 100209

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology



Maternal outcomes related to Genetic and epigenetic Variation in the oxytocin system: A scoping review

Sarah R. Weinstein [a,*], Elise N. Erickson [a], Rodin Molina [b,c], Aleeca F. Bell [a]

[a] University of Arizona College of Nursing, Tucson, AZ, USA
[b] Frontier Nursing University, Hyden, KY, USA
[c] BabyMoon Inn Birth Center, Tucson, AZ, USA

ARTICLE INFO

Keywords:
Oxytocin
DNA methylation
Genetics
Breastfeeding
Mental health
Maternal behavior

ABSTRACT

Purpose: In this scoping review, we synthesize the literature on oxytocin and oxytocin receptor genetic and epigenetic variation in relationship to breastfeeding, maternal caregiving behavior, and maternal mental health.
Methods: A literature search was conducted in early 2022, and updated in 2023, utilizing the PRISMA scoping review reporting method, using the following MeSH headings and key terms: oxytocin, oxytocin receptor, genetics, epigenetics, methylation, pregnancy, postnatal, breastfeeding, lactation, mother-infant relations and perinatal outcomes. The search was conducted using PubMed, EMBASE, CINAHL, Google Scholar, SCOPUS, and the Cochrane Library. Inclusion criteria included: human literature which was peer reviewed and found in primary sources, printed in the English language. In addition, the study must have reported genetic/epigenetic data in either the oxytocin or oxytocin receptor gene (maternal or infant up to 12 months after birth) in relation to a breastfeeding, maternal caregiving behavior or a maternal mental health outcome. There was no date limitation. Four authors reviewed studies for eligibility. Data was extracted using a structured data extraction form.
Results: A total of 23 studies met inclusion criteria for this review (breastfeeding n = 4, maternal caregiving behavior n = 7, and maternal mental health n = 16). Seventeen papers reported on oxytocin or oxytocin receptor genotype and nine reported epigenetic associations (namely DNA methylation). These totals are greater than 23, as studies reported on multiple outcomes. One paper assessed the interaction between genotype and methylation. While a number of genotype variations were reported, the single nucleotide polymorphism rs53576 on the oxytocin receptor gene was the most studied. Overall, variation in this polymorphism was related to postnatal depression symptoms. Among numerous epigenetic markers, site −934 was the most studied methylation site, and methylation status was associated with maternal depression and maternal caregiving behavior outcomes. Results suggest that early life experiences impact adult maternal caregiving behaviors and mental health outcomes, and vary based on genetic vulnerability. Breastfeeding outcomes were minimally studied.
Conclusion: This scoping review found that genetic and epigenetic variation at the oxytocin and oxytocin receptor genes were associated with maternal caregiving behavior and mental health, likely through complex gene and environment interactions. The findings suggest that maternal early life experiences and stress impact later caregiving behaviors and mental health in the postnatal period. The findings highlight potential pathways by which environment, experiences, and genes interact to impact maternal caregiving behavior and maternal mental health.

1. Introduction

The oxytocin (OXT) system plays a central role in perinatal processes that impact trajectories of infant, child, and family well-being [1]. The OXT system includes the oxytocin neuropeptide/hormone as well as the oxytocin receptor (OXTR) which is required to bind OXT and exert effects within the cell or communicate between neurons. OXT is a nine-amino acid peptide which is produced and acts within the hypothalamus as well as throughout the brain and peripheral body [2]. The OXTR is a G-protein-coupled receptor which sits on the plasma

* Corresponding author.
E-mail address: sarahweinstein@arizona.edu (S.R. Weinstein).

https://doi.org/10.1016/j.cpnec.2023.100209
Received 11 July 2023; Received in revised form 11 September 2023; Accepted 12 September 2023
Available online 26 September 2023

membrane of cells located throughout the body, including in the uterus, breast, and brain tissues, as well as the placenta, various immune cells, and the gastrointestinal tract, among others [2–4]. The OXT system is highly conserved among mammals, and has been considered an essential adaptive system that, through various evolutionary pressures, became a key regulator of sociality, danger recognition, fear modulation, and stress reactivity [3]. Extensive research supports that the OXT system shapes both biological (e.g., labor, birth, lactation, stress response modulation) and behavioral (e.g., human socialization, empathy, bonding, dyadic synchrony, parental behaviors) processes [1,5–16].

The candidate genes most often examined in relationship to the OXT system are the oxytocin peptide gene (*OXT*), the oxytocin receptor gene (*OXTR*), and *CD38*, a nicotinamide adenine dinucleotide ectoenzyme involved in OXT secretion [7,17]. *CD38* has been shown to be involved in OXT signaling (primarily in studies with mice) [18]; however, the majority of human studies including *CD38* focus on psychopathology, specifically autism [7]. Additionally, *CD38* has a wide range of roles in immunomodulation including metabolic dysfunction, infection, and aging [19]. Given the scarce literature on *CD38* in human postnatal behaviors, this signaling pathway ecto-enzyme was not included in our review of postnatal outcomes related to the genes of OXT and its receptor.

1.1. Variation among OXT/OXTR genes

OXT system function is influenced by an individual's variation in their genetic code or epigenetic modification of that code [20]. These differences may be found within or at the oxytocin peptide gene (*OXT)* and the oxytocin receptor gene (*OXTR)* [21]. The molecular differences are connected to functional differences in the OXT system and downstream health outcomes [21–29]. The study of genetic variation in the OXT system has predominantly been focused on single nucleotide polymorphisms (SNPs), which are heritable, single base-pair variations at specific loci. Various *OXTR* SNPs have been studied in connection with OXT-linked psychosocial outcomes [28,30]. Because SNPs represent changes in the DNA code, they could influence the product of gene expression, which may result in functional differences in the effectiveness of the OXTR protein or OXT binding, and subsequent cellular and downstream responses.

The study of epigenetic variation in the OXT system has predominantly focused on DNA methylation (DNAm). Methylation refers to the addition of methyl groups (CH_3) at certain locations within DNA (typically Cytosine-Guanine rich regions of DNA). DNAm in promoter regions of genes typically inhibit gene transcription. However, the relationship between the measurement of DNAm and gene expression may not be straightforward. For example, additional chemical marks can modify already-methylated DNA, which functionally overrides methylation and permits gene expression (e.g., hydroxymethylation) [31]. This distinction and limited methodological differentiation makes interpretation of findings more complex than previously thought. Epigenetic modifications at OXT system genes may represent adaptive mechanisms (either amplifying or dampening the OXT system) to environmental exposures in the body of literature reviewed here. Importantly, these studies all utilized peripheral markers of the OXT system either from blood or saliva samples. Although *OXTR* and *OXT* are not expressed in all tissues, human and animal studies have consistently demonstrated correlation between peripheral and central DNAm in the OXT system supporting the utilization of peripheral OXT system DNAm as a proxy for central DNAm [27,32].

1.2. Setting the stage: genetic & epigenetic research in the context of health equity & antiracism

Scientific discourse has the power to perpetuate or disrupt historical legacies of racism that are inherent in the social constructs of racialized differences between groups [33]. Research that involves genetic and epigenetic exploration must be conducted with social consciousness to ensure that 1) embodied social inequity is included in frameworks that describe these phenomena [34], 2) genetic data are examined with an anti-racist lens (i.e. explicit acknowledgment of race as a social construct [35] and an active commitment to combat a biased interpretation of data), and 3) genetic data are utilized for understanding variation within populations and are considered probabilistic not deterministic tools.

As we will demonstrate, upstream causes of *OXTR* epigenetic reprogramming may include environmental sources of stress conceptualized as "social determinants of health." [34] Epigenetic markers have been shown to differ by levels of chronic stress, including poverty, childhood abuse, and exposure to racism [36–39]. Use of epigenetic biomarkers can therefore be useful in studying the biopsychosocial impact (embedding of environmental experiences described as a biological embodiment of stress [34,40–42]) of the life course and inequitable systems on health. Whether epigenetic changes are modifiable in the individual is also an important opportunity for basic and translational research, and for those interested in working toward improving health outcomes among at-risk groups. Finally, examining DNAm in the context of genetic variation affords the opportunity to examine innate vulnerability to/protection from the effects of social stress—or *within* group variation.

Thus, a misapplication in the genetic literature at large, not unique to the studies in this review, is the use of racial categorization to analyze genetic data. This can be problematic as racial groupings are fundamentally a social construct and limited by false categorizations and restricted data collection where participants generally have only government or census-derived categories to choose from [35]. A focus on geographic ancestry, implemented by some studies, is likely a more encompassing and accurate picture of population distinctions. More specific or accurate descriptions are preferred (e.g., "American or Alaskan Native" rather than "other") as are inclusive versus exclusive terms (e.g., "African American or Black" rather than "non-white"). Where appropriate, self-reported race is ideal as race impacts lived social experiences [33].

Our hope is that this scoping review supports the interest of other researchers who wish to understand and describe the potential relationships among genetic and epigenetic alterations in the OXT system and maternal/infant outcomes in order to promote maternal and child health in relevant and equitable ways. More basic and translational science across diverse samples of participants is needed to generate more concrete conclusions regarding SNPs and cytosine-phospho-guanine (CpG) sites of interest and equity in perinatal outcomes.

1.3. Existing literature on OXT/OXTR linked outcomes

The majority of research on genetic and epigenetic variations of *OXT* and *OXTR* has focused on psychological outcomes, linking *OXTR* methylation with conditions such as autism, obsessive-compulsive disorder, and impaired attachment [28,30]. Early life experiences impact methylation and subsequent gene expression, most clearly demonstrated by several seminal papers in rodent models of maternal care [43–51]. This body of literature highlights DNAm as an important focus of research on OXT dependent processes and health.

Oxytocin is integral to the processes of lactation and breastfeeding, maternal caregiving behavior, and maternal mental health [1,11,52]. Despite the role of the OXT system in perinatal physiology [2], few *OXT/OXTR* studies have focused on perinatal outcomes aside from postnatal depression, which is defined in this review either as a clinical diagnosis or elevated symptoms. By identifying genetic and epigenetic variations at *OXT* and *OXTR* loci linked to poor outcomes in these domains, researchers may be able to understand mechanisms behind certain conditions and/or target interventions that are informed by the understanding of a person's innate OXT system. This work can also inform us of the upstream environmental causes of epigenetic change that may confer risks or vulnerabilities. The primary objective of this

scoping review is to present the extant literature that investigates *OXT* and *OXTR* genetic and epigenetic variations in relationship to breastfeeding, maternal caregiving behavior, and maternal mental health.

2. Methds

2.1. Search strategy

We conducted a broad comprehensive literature review in 2022, utilizing the PRISMA reporting method. As this was not a systematic review, no protocol was registered. In consultation with a health sciences librarian, our search used MeSH headings and key terms, including: oxytocin receptor, genetics, epigenetics, methylation, pregnancy, postpartum, breastfeeding, lactation, mother-infant relations and perinatal outcomes including maternal mental health. We searched PubMed, Embase, CINAHL, Google Scholar, Scopus, and the Cochrane Library. Listed below is the full search strategy for PubMed as an example.

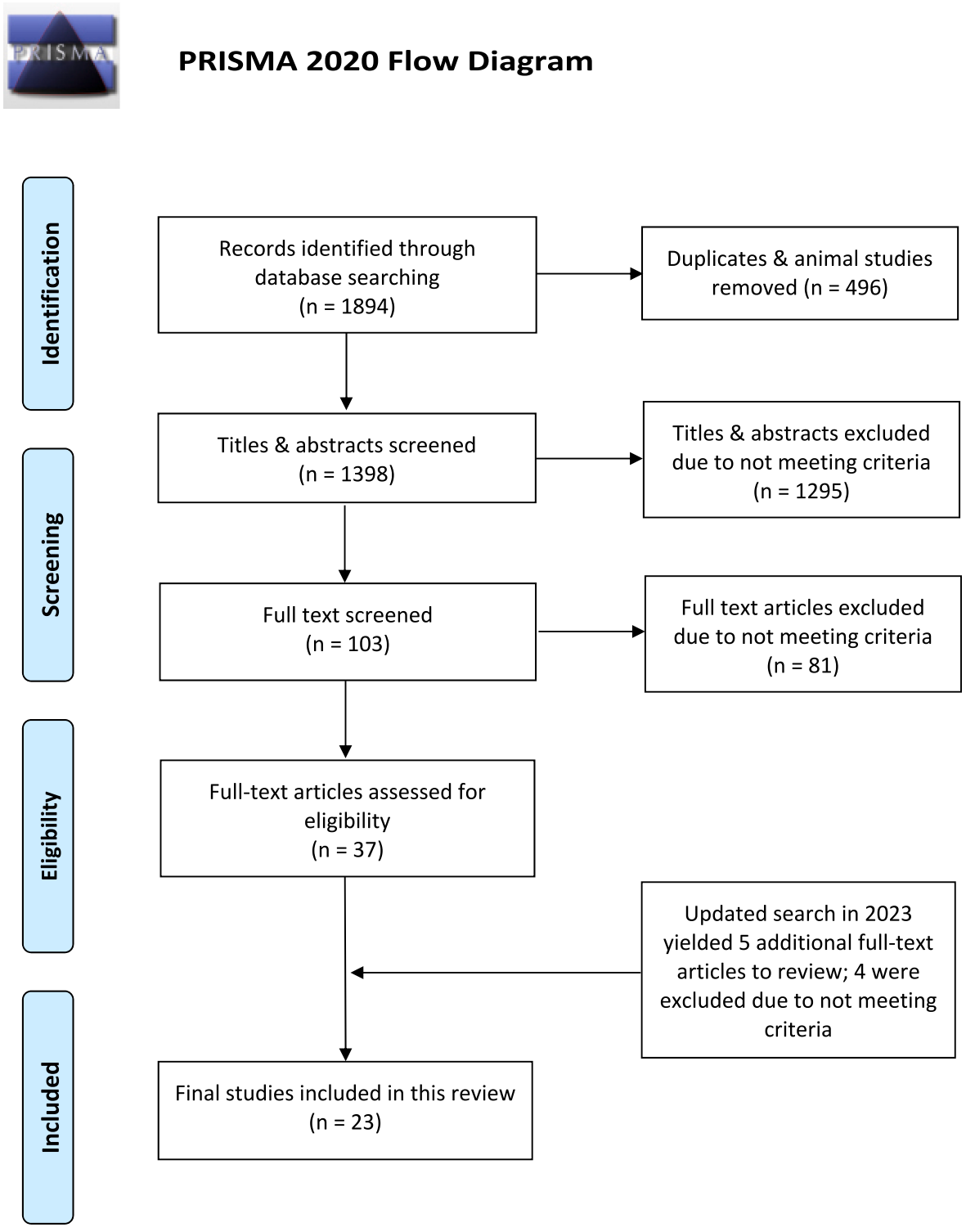


Fig. 1. Prisma 2020 flow diagram.

(((oxytocin [Title/Abstract] OR "oxytocin receptor*" [Title/Abstract] OR OXTR [Title/Abstract]) OR ("Oxytocin" [Mesh] OR "Receptors, Oxytocin" [Mesh])) AND ((genetics [Title/Abstract] OR genetically [Title/Abstract] OR epigenomics [Title/Abstract] OR "genetic epigenesis" [Title/Abstract] OR methylation [Title/Abstract] OR "single nucleotide polymorphism" [Title/Abstract] OR SNP [Title/Abstract] OR genes [Title/Abstract] OR genotype [Title/Abstract] OR epigenetic [Title/Abstract]) OR ("Genetics" [Mesh] OR "Epigenomics" [Mesh] OR "Epigenesis, Genetic" [Mesh] OR "Methylation" [Mesh] OR "Polymorphism, Single Nucleotide" [Mesh] OR "Genes" [Mesh])) AND (("Pregnancy Outcome" [Mesh] OR "Pregnancy Complications" [Mesh] OR "Breast Feeding" [Mesh] OR "Maternal Behavior" [Mesh] OR "Infant Behavior" [Mesh] OR "Depression, Postpartum" [Mesh] OR "Postpartum Hemorrhage" [Mesh] OR "Dystocia" [Mesh] OR "Postpartum Period" [Mesh] OR "Obstetric Labor, Premature" [Mesh] OR "Hypertension, Pregnancy-Induced" [Mesh] OR "Labor, Obstetric" [Mesh] OR "Pregnancy" [Mesh] OR "placenta diseases" [MeSH Terms]) OR (breastfeeding [Title/Abstract] OR "postpartum depression" [Title/Abstract] OR "postnatal depression" [Title/Abstract] OR "mother-infant bond*" [Title/Abstract] OR "mother-infant relation*" [Title/Abstract] OR preeclamp*[Title/Abstract] OR "postpartum complication*" [Title/Abstract] OR "mothering" [Title/Abstract] OR "postpartum hemorrhag*" [Title/Abstract] OR "postnatal hemorrhag*" [Title/Abstract] OR Dystocia [Title/Abstract] OR "lactation" [Title/Abstract] OR "pregnancy complication" [Title/Abstract] OR birth [Title/Abstract] OR "preterm labor" [Title/Abstract] OR pregnancy [Title/Abstract] OR "Cesarean Section" [Title/Abstract] OR "Placental Insufficiency" [Title/Abstract] OR "Retained Placenta" [Title/Abstract] OR "Placenta Previa" [Title/Abstract] OR "Placenta Accreta" [Title/Abstract] OR "Chorioamnionitis" [Title/Abstract] OR "Abruptio Placentae" [Title/Abstract]))

2.2. Article eligibility criteria

As the literature on these topics is limited, and because genotyping and epigenetic assessment utilize relatively new technologies, all publications meeting criteria were included, regardless of publication date. Perinatal outcomes include the broadest definition of the term, and so referred to any outcome associated with pregnancy, labor, birth, the postnatal period, or lactation. Literature on various other psychologic, psychiatric, or social outcomes not directly related to early maternal caregiving behavior or mental health (e.g., autism spectrum disorder) were excluded. Articles not available in English or those not peer-reviewed were also excluded.

2.3. Selection process

The search initially yielded 1894 titles (Fig. 1). After removing 496 titles for duplicates and animal studies, we screened 1398 abstracts. All reviewers engaged in a norming process before screening titles and abstracts, completing full-text review, and starting data extraction to establish a process of resolving discrepancies and ensuring accuracy. Two independent reviewers were involved at each stage of screening and reviewing. Reviewers utilized an excel spreadsheet for reviewing decisions at each stage. We extracted data using a customized, structured data extraction form. All reviewers were involved in the data extraction process with each article assigned to an individual reviewer; any questionable data were noted and resolved with group consensus. After removing 1295 abstracts that did not meet inclusion criteria, we screened 103 full text articles, of which 81 were removed due to not meeting inclusion criteria. Conducting an updated search in 2023 yielded five additional full text articles to review, and only one met our inclusion criteria. In conclusion, 23 full text articles met inclusion criteria for this scoping review.

3. Results

3.1. Overview

The results from the 23 articles included in this scoping review are presented first by *OXT/OXTR* SNP variations and DNAm measures, and second by outcome categories. Only one study reported on the interaction of SNP variation and DNAm [53]. Outcome categories were determined by author consensus (Table 3) and grouped by Breastfeeding (BF), Maternal Caregiving Behavior (MB) or Maternal Mental Health (MMH). Given the nature of the review, the studies include a wide variety of measures, methylation sites, and SNPs. While results are heterogeneous, we describe overall patterns in each of the subsequent sections.

3.1.1. Study characteristics

Of the 23 studies included in this review, 19 were cohort designs and four were cross sectional designs (Table 2) [22,54–56]. Four studies utilized retrospective [57], secondary [58,59], or post hoc analysis of previously collected data [60]. Sample sizes ranged from 39 to 2112 participants, and in some cases resulted from merging different study cohorts or data from different countries. Eight studies assessed mother-infant dyads [54,56,59,61–65], while the remainder enrolled only mothers (see Table 2).

3.2. SNP studies

3.2.1. Genetic variants studied

Most studies (n = 17) examined a small number of SNPS on either *OXT* or *OXTR* (Table 4). However, one paper analyzed a panel of 19 *OXT* and 137 *OXTR* SNPs [57], and another paper reported on a panel of 19 *OXTR* SNPs [55], illustrating the amount of naturally occurring variation in the genetic code for *OXTR/OXTR*. The most commonly studied SNP was *OXTR* rs53576 followed by *OXTR* rs1042778, rs2254298, and rs237885. Although many of these SNPs are located within introns, or non-coding sequences (Fig. 2), they can play roles in gene regulation [66].

3.2.2. Breastfeeding

Four studies included breastfeeding outcomes [54,57,58,67], and there was significant variability in how breastfeeding was measured and which SNPs were studied. Colodro-Conde et al. retrospectively reviewed the association between a series of *OXT* and *OXTR* SNPs and breastfeeding duration, however, no associations withstood multiple testing statistical corrections [57]. Jonas et al. found that maternal depression significantly mediated the relationship between shorter breastfeeding duration and higher levels of early life adversity for those with the CC versus AA/AC genotype of *OXT* rs2740210 [67]. Kovacs noted a significant relationship among exclusive breastfeeding**,** *infant* genotype at *OXTR* rs53576, and maternal depression [54]. Mothers who did not exclusively breastfeed were more likely to report higher depression scores, and mothers of GG infants had higher scores than those of AA infants. However, if mothers of GG infants were exclusively breastfeeding, their depression scores were lower, suggesting a protective function of breastfeeding exclusivity. Lucas et al. were the only authors

Table 1
Key terms & definitions.

Breastfeeding (BF)	breastfeeding, nursing, lactation, chest-feeding
Maternal Caregiving Behavior (MB)	engagement, intrusiveness, vocalizations, attachment, interactions
Maternal Mental Health (MMH)	depression or anxiety diagnosis or symptoms, psychosocial stress, acculturation stress
Early life experiences	experiences during uterine & early extra-uterine life (time periods vary), parenting or caregiving, adverse childhood experiences of the mother during her own childhood

Table 2
Study characteristics.

First Author, Year	Study Aim	Study Design	Sample		Outcome	OXT/OXTR Measures
			Participants	*Biological Sample Source*		
Asherin, 2020	Association between variations in maternal *OXTR* rs53576 genotype and maternal symptoms of depression Association between infant's *OXTR* rs53576 genotype and maternal depression Whether and how the infant's *OXTR* genotype interacts with maternal *OXTR* genotype and depressive symptoms Test for a mediating role for infant temperament	Cross-sectional	US (national) N = 104 mother-infant dyads Ancestry or race/ethnicity: majority "White; " 19% "Minority Status"	Saliva/buccal cells	Severity of depression symptoms 4–14mo postpartum (PP)	Single Nucleotide Polymorphism (SNP): *OXTR* rs53576
Bell, 2015	Impact of individual epigenetic and genetic variability at *OXTR* on the development of postpartum depression (PPD)	Case-control nested within Avon Longitudinal Study of Parents and Children (ALSPAC)	UK n = 269 cases n = 276 controls Ancestry or race/ethnicity: "demographically similar to the UK population"	Blood (7–40 wks gestation)	Elevated symptoms of depression 8 wks. PP	*OXTR* DNA methylation (*OXTR*m): CpG −934 (8769120) Reference genome: 38 SNP: *OXTR* rs2254298 *OXTR* rs53576
Bhatti, 2019	Moderation of the interaction between low social support (particularly paternal support) and postnatal depression symptoms by *OXTR* SNP rs53576	Cross-sectional	US (CA) N = 220 women Ancestry or race/ethnicity: "53% White, 28% Latina, 11% Asian, 1% African-American/Black, 7% Other or more than one"	Saliva or blood	PPD symptoms 12 or less postnatal months	SNP: *OXTR* rs53576
Cao, 2021	Exploration of a biopsychosocial model incorporating gene × environment interactions and covariates to predict PPD symptoms.	Cohort, prospective (third trimester through 2 years PP)	US (Southeast) N = 198 women Ancestry or race/ethnicity: "112 self-identified as European American and 86 as African American"	Saliva	PPD 1 yr. PP	SNP: *OXTR* rs53576
Colodro-Conde, 2018	Association of a range of *OXT* and *OXTR* SNPs and BF duration	Two independent cohorts, data retrospectively pulled from longitudinal samples	Spain (Murcia Twin Registry) n = 580 Australia (QIMR Berghofer Medical Research Institute) n = 2112 Independent unselected samples of twin female mothers born 1940s–1980s with a portion of the second cohort born in the late 1800s–1960s Ancestry or race/ethnicity: European ancestry	Spain: blood or saliva Australia: saliva	BF duration and exclusivity	SNP: *OXT:* Panel of 19 SNPs *OXTR:* Panel of 137 SNPs
Dewell, 2018	Association of genotype with high or low prenatal psychosocial distress	Cohort, prospective (initiated in second trimester of pregnancy, outcomes assessed through first PP year)	Canada n = 25 low prenatal distress n = 25 high prenatal distress women (from All our Families pregnancy cohort) Ancestry or race/ethnicity: majority "Caucasian"	Whole blood (17–23 wks gestation)	Prenatal psychosocial distress (depression, anxiety, stress)	SNP: *OXTR* rs237885
Feldman, 2013	Impact of parental caregiving on offspring OT levels and social reciprocity and allelic variation	Prospective, longitudinal cohort (3 years)	Israel N = 160 triads (mothers, fathers, first born infant) Ancestry or race/ethnicity: "Caucasian"	Blood from parents initially, salivary OT at 3 yrs.	Mothering behavior at 6 months	SNP: *OXTR* rs1042778 *OXTR* rs2254298
Galbally, 2018	*OXTR* methylation of the placenta in women with depression in pregnancy, as well as the impact of antidepressant use on this outcome	Cohort, Case-control	Australia N = 239 women (from Mercy Pregnancy and Emotional Wellbeing Study) [n = 43 women on antidepressant medication (15 of these did not meet dx for major depression at	Maternal plasma, umbilical cord blood at birth	Placental *OXTR* methylation in depression	*OXTR*m: 16 CPG sites, ch3:8810680–8810890 Reference genome: hg19 (inferred by locations provided)

(*continued on next page*)

Table 2 (*continued*)

First Author, Year	Study Aim	Study Design	Sample		Outcome	OXT/OXTR Measures
			Participants	*Biological Sample Source*		
			recruitment) n = 52 cases major depressive disorder (n = 24 untreated at recruitment) n = 172 controls] Ancestry or race/ethnicity: not available			
Incollingo Rodriguez, 2022	Role of the oxytocin system in response to acculturation stress, specifically looking at anxiety and depression symptoms in Latina women living in the US	Cohort, prospective (24–32 wks Gestation through first PP year)	US (NC) N = 148 Latina women Ancestry or race/ethnicity: majority country of origin Mexico	Venous blood, buffy coat (DNAm)	Depression and anxiety symptoms and exposure to acculturation 46 postnatal wks.	*OXTR*m: CpG −934 Reference genome: not indicated SNP: *OXTR* rs53576
Jonas, 2013	Relationship between *OXT/OXTR* SNPs and BF duration, maternal mood, childhood trauma	Prospective cohort, data from two cohorts (one replication) from MAVAN (Maternal Adversity, Vulnerability, and Neuro-development Study)	Canada n = 201 women (Hamilton) n = 151 women (Montreal-replication) Ancestry or race/ethnicity: majority of "Caucasian" decent; ethnicity used as covariate in regression modeling	Buccal	BF duration, PPD at 3, 6, 12 PP months	SNP: *OXT* rs2740210 *OXT* rs4813627 *OXTR* rs237885
Julian, 2019	Effect of *OXTR* SNPs, childhood maltreatment, and their interaction in predicting parenting	Secondary analysis of longitudinal studies: Maternal Anxiety During Childbearing Years (MACY) & Perinatal Infant Mother Attachment Cortisol Study (PIMACS)	US N = 100 dyads (81 MACY, 19 PIMACS) Ancestry or race/ethnicity: majority self-reported "White"	Saliva-mothers	Observed parenting behavior, self-report parenting at 7mo. PP	SNP: *OXTR* rs1042778 *OXTR* rs53576
Kimmel, 2016	Interaction between *OXTR* DNA methylation and maternal traumatic experiences and the association of these variables with development of PPD. Relationship between PPD diagnosis and *OXTR* gene expression observed in pregnancy.	3 Cohorts, (first two samples listed were prospective)	US & Germany N = 51 Johns Hopkins Prospective PPD sample; looking to identify genetic and clinical characteristics preceding PPD N = 63 [n = 18 always depressed women, n = 28 antenatally euthymic, n = 17 postpartum onset depression cases] Publicly available gene expression data collected by Mehta et al., in 2014 at Emory N = 240 Franconian Maternal Health Evaluation Studies (FRAMES) cohort; assessing genetics and PP outcomes Ancestry or race/ethnicity: majority "Caucasian"	Blood	PPD	*OXTR*m: CpG ch3:8810078 & 8810069 Reference genome: hg19 SNP: *OXTR* rs53576
Kovacs, 2020	Relationship between maternal depression and infant *OXTR* genotype as moderated by BF	Cross-sectional, during a single study visit	US (CO) N = 58 dyads, 3–7mo infants Ancestry or race/ethnicity: majority "not a minority"	Saliva/buccal cell-only infant genotype reported	Exclusive BF as moderator for maternal depression measured at visit	SNP: *OXTR* rs53576
Krol, 2019	Influence of early nurture on the development of the oxytocin system	Cohort, longitudinal	Germany N = 101 dyads (5mo and 18mo visits) Ancestry or race/ethnicity: "Western European Ancestry"	Saliva	Infant DNA methylation, maternal engagement at 5 months PP	*OXTR*m: CpG −924 Reference genome: hg38
Lee, 2019	Association between maternal psychological symptoms and fourteen candidate genes among women with GDM	Post hoc sub analysis of a cross-sectional study	Malaysia N = 343 women with GDM Ancestry or race/ethnicity: "Native Malaysian"	Blood	Depression, anxiety, stress in 2nd or 3rd trimester	SNP: *OXTR* rs53576

(*continued on next page*)

Table 2 (*continued*)

First Author, Year	Study Aim	Study Design	Sample		Outcome	OXT/OXTR Measures
			Participants	*Biological Sample Source*		
Lucas, 2021	Associations between breast and nipple pain and candidate SNPs in breastfeeding women	Secondary analysis	US (northeast) N = 56 women [n = 26 from intervention group n = 30 from control group] Ancestry or race/ethnicity: majority "white"/"not Hispanic or Latino"	Buccal	Baseline pain assessment prior to hospital discharge: nondominant arm for cutaneous, vibration, and pressure sensitivity and pressure pain thresholds. Nipple/breast pain at 1, 2, & 6 wks. PP	SNP: *OXTR* rs53576 *OXTR* rs2254298
Mehta, 2016	Relationships between serum OT, *OXTR* genetic variations, and maternal behavior	Cross sectional	Australia N = 96 women (subsample of women with genetic information available for analysis) Ancestry or race/ethnicity: "Caucasian 47.9%, Asian 33.3%, Arab 12.5%, Other 6.3%"	Blood	Maternal behavior, sensitivity, separation anxiety at an average of 30 wks Gestation & 3mo. PP	SNP: *OXTR*: Panel of 19 SNPs including rs53576 rs2254298 rs1042778 rs968389 used to calculate genetic risk scores
Mileva-Seitz, 2013	Variations in *OXT/OXTR* SNPs and maternal care Interaction between *OXT* SNPs on maternal instrumental care and PPD	Cohort, longitudinal	Canada N = 187 women [n = 58 agreed to recorded interaction sessions] Ancestry or race/ethnicity: "Caucasian"	Buccal cells	Maternal depression at 12–24 wks Gestation & 6 mo. PP. Maternal-infant interactions at 6 mo. PP	SNP: *OXTR* rs237885 *OXT* rs2740210 *OXT* rs4813627
Robakis, 2020	Biological pathways (patterns of DNA methylation) linking early life adversity and insecure attachment style to perinatal depression	Cohort, longitudinal	US (Northern CA) N = 124 women, clinical sample N = 54 women, genetic sample (pregnant participants recruited from psychiatric and OB clinics) Ancestry or race/ethnicity: "Caucasian 60.7%, East Asian 10.7%, South Asian 7.1%, Hispanic 7.1%, African American 0%, Multiracial 14.3%"	Buccal swab (third trimester of pregnancy)	Perinatal depression via EPDS in third trimester of pregnancy and monthly x 6 PP mo.	*OXTR*m: 151 distinct CpG sites Chr3: between 8806364 & 8811271 Reference genome: hg19
Toepfer (1), 2019	Examine DNAm changes at OXT promoter region throughout pregnancy as a predictor of mothering behavior PP	Cohort, prospective	US (CA) N = 107 dyads Ancestry or race/ethnicity: majority non-Hispanic white	Whole blood	DNAm early, mid, & late pregnancy Maternal intrusiveness (6 mo. PP)	*OXT*m (promotor region): CpG 16887334 Chr20:3052151 Reference genome: hg19
Toepfer (2), 2019	Role of *OXTR* rs237895 as a moderator of the relationship between childhood maltreatment and maternal behavior Association between maternal behavior and offspring attachment security	Cohort, prospective	US (CA) N = 110 women with genotyping (99 women at 6 months) N = 86 infants at 12 months Ancestry or race/ethnicity: "Non-Hispanic white 43.1%, Hispanic white 37.3%, Asian 6.9%, Other 12.8%"	Fasting blood samples (first trimester of pregnancy)	Maternal behavior (6 mo), infant attachment (12 mo)	SNP: *OXTR* rs237895
Unternaehrer, 2016	Relationship maternal psychosocial adversities and cortisol levels during pregnancy and cord blood DNA methylation of the *OXTR*	Cohort, longitudinal	Switzerland N = 39 women	Cord blood collected immediately after birth (whole blood); Salivary cortisol (cortisol awakening response & diurnal cortisol profiles)	DNA methylation in cord blood	*OXTR*m: CpG Chr3:8809275-8809534 Reference genome: hg19 (inferred by locations provided)
Wiley, 2022	Relationship between maternal prenatal psychological distress and infant DNAm and diurnal cortisol at 12mo.	Cohort, longitudinal (enrolled in an RTC on parenting support program)	Brazil (western Sao Paulo) N = 80 dyads (recruited in pregnancy, ages 14–19, "low socioeconomic status") Ancestry or race/ethnicity: not described	Infants: saliva for DNAm & diurnal cortisol Mothers: hair cortisol in pregnancy	Maternal stress and anxiety at 16-18- and 30-32-weeks gestation Infant DNAm at 12mo.	*OXTR*m: OXTR1: 8808467-8810658 OXTR2: 8808058-8810304 Reference genome: hg19

Table 3
Outcomes, measures & findings.

Author, Year	Postnatal Outcome Category			Measures	Statistics	Major Findings
	Breast-feeding	*Maternal Mental Health*	*Maternal Caregiving Behavior*			
Asherin, 2020		x		Beck Depression Inventory (BDI), Infant Characteristics Questionnaire, Abbreviated Dyadic Adjustment Scale (ADAS)	Analysis of Covariance (ANCOVA)	Depressive symptom scores were significantly higher for maternal *OXTR* rs53576 GG in comparison to A carriers (*P*=*.01*) until controlling for covariates (*P* > *.58)*. Maternal depressive symptom scores were significantly higher for GG infants irrespective of maternal genotype (*P*=*.05*). No significant interaction between maternal and infant genotype (*P*=*.42*).
Bell, 2015		x		Edinburgh Postnatal Depression Scale (EPDS)	Conditional Logistic Regression	In women without antenatal depression, G/G carriers (*OXTR* rs53576) had 2.6 greater odds of postpartum depression (PPD) with every 10% increase in methylation (*OXTR* CpG −934) versus A carriers (95% CI, 1.37–5.03; P=*.026*). This relationship was not significant among A carriers (odds ratio [OR] 1.0, 95% CI, 0.58–1.73). Neither methylation (*P*=*.30*) nor genotype alone (*P*=*.69*) were associated with PPD.
Bhatti, 2019		x		Perceived family social support; EPDS; Perceived Stress Scale (PSS)	Multivariate Linear Regression	Interaction between maternal genotype at *OXTR* rs53576, perceived stress, and father support predicted PPD (*P*=*.008*, 95% CI, .22–1.44). Paternal support buffered PPD symptoms in the setting of higher perceived stress for GG genotypes (*P*=*.010*, 95% CI, −1.14 to −0.16), but not for AG (*P*=*.760*, 95% CI, −0.65-0.88) or AA genotypes (*P*=*.061*, 95% CI, -.058-2.37).
Cao, 2021		x		The 20-item Center for Epidemiologic Studies–Depression Scale; Childhood Trauma Questionnaire (CTQ)	Chi-square, Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA), Standardized Root Mean Square Residual (SRMR)	No significant associations between *OXTR* rs53576 genotpye and maternal depression in a model also incorporating depamine receptor genotype, childhood maltreatment, relationship satisfaction, and other covariates (*P*=*.19)*.
Colodro-Conde 2018	x			Participatnts were asked to report BF duration in months for each child, and if BF was "partial or full"	Linear Regression, Meta-analysis	Across 19 *OXT* SNPs and 137 *OXTR* SNPs, no association with breastfeeding duration after multiple testing correction. Top SNP hits: OXTR rs237899, rs237900, rs237889, rs53576, rs62243369, rs62243370, rs2254298, rs2254295, rs237915, rs237902, rs401015, rs180789, rs11706648, rs2268491, rs237913, rs2270464, rs3806675, rs13319411, rs4686302; OXT: rs2740197
Dewell, 2018		x		Edinburgh Postnatal Depression Scale (EPDS), Spielberger State Anxiety Inventory (SSAI), Perceived Stress Scale (PSS)	Chi-square, Fisher's exact, *t*-test, Analysis of Variance (ANOVA), Binary Logistic Regression	*OXTR* rs237885 genotype distribution was not significantly different between the low and high prenatal psychosocial distress groups (*P* = .125) Participants with GG genotype were less likely to be in high prenatal distress group after controlling for maternal age and income (*P* = .037); maternal age, and lower income were associated with prenatal psychosocial distress.
Feldman 2013			x	Observed engagement in parenting behaviors	ANOVA, Pearson correlations	Mothers with G/G on OXTR rs2254298 showed diminished early parental care (*P*=*.045*). Early parental care was associated with higher parent OT (*P*=*.01*)

(*continued on next page*)

Table 3 (*continued*)

Author, Year	Postnatal Outcome Category			Measures	Statistics	Major Findings
	Breast-feeding	*Maternal Mental Health*	*Maternal Caregiving Behavior*			
Galbally, 2018		x		Structured Clinical Interview for DSM-IV (SCID), EPDS, Plasma levels of antidepressant drugs in maternal serum and cord blood at birth	Zero-order Bivariate Pearson's correlations, ANOVA, Multiple Regression Modelling	Overall, placental *OXTR*m was lower when the pregnant participant took antidepressant medication during pregnancy compared to individuals with or without depression symptoms,who were not taking antidepressants (*P=.039*). Among participants exposed to antidepressants, controlling for third trimester symptoms, methylation measured in infant cord blood was higher with greater measured concentrations of SSRI medication (*P=.019*)
Incollingo Rodriguez, 2022		x		Everyday Discrimination Scale (EDS), Bidimensional Acculturation Scale (BAS), General *Anxiety Disorder Questionnaire (GAD-7)*, EPDS	Regression analyses	In mothers with low OXT peptide & low *OXTR*m, acculturation was associated with postnatal depression and anxiety. Higher self-reported discrimination and acculturation were associated with postnatal depression and anxiety among G carriers (*OXTR* rs53576) (acculturation *P=.010*, discrimination *P=.001*), compared to AA genotype.
Jonas 2013	x	x		CTQ, Center for Epidemiological Studies Depression Scale (CES-D), BF in weeks (continuous) & dichotomous exclusivity at 3 & 6 months; partial BF at 12mo	Hierarchical multiple regression	In C/C genotype, OXT rs2740210 significantly interacted with early life adversity to influence breastfeeding duration (overall *P=.021*; interaction effect *P=.023*) and depression ($P \leq .001$; interaction effect *P=.002*). Maternal depression mediated the inverse relationship between BF duration and early life adversity.
Julian, 2019			x	CTQ, SCID, Infant–Parent Coding System, Parent Infant Interaction Scale, Postpartum Bonding Questionnaire (PBQ)	Bivariate correlations, MANOVA, MANCOVA, χ [2] testing, Bonferroni corrections	For *OXTR* rs1042778 mothers with T/T genotype scored lower behavioral sensitivity, lower engagement, higher intrusiveness, and more frequent frightened/frightening behavior than T/G or G/G mothers ($P < .01$). Genotype interacted with childhood trauma history such that mothers who had experienced childhood trauma were more likely to demonstrate frightened/frightening behavior if they were T/T on rs1042778 relative to G-carrying mothers (P < .01) For *OXTR* 53576, A-carriers reported lower rates of hostility ($P < .01$)
Kimmel, 2016		x		BDI, Hamilton Depression Rating Scale (HDRS), EPDS	*t*-test; linear regression	Cases with postpartum depression who were also depressed prenataly, had lower levels of *OXTR*m than cases who were not depessed prenatally (*P=.035*). For women who did not develop postnatal depression, childhood abuse increased *OXTR*m (*P=.045*). Women with HDRS scores >/14 had lower *OXTR*m levels (*P=.035*). Linear Regression including abuse, PPD, Antenatal Depression Status, Abuse × PPD interaction improved model fit, *P=.009*.
Kovacs 2020	x	x		BDI, *Panic Disorder Severity Scale (PDSS),* mode of infant feeding	χ [2] testing, *t*-test,	Exclusive BF was significantly associated with lower depression scores ($P < .05$). Mothers of rs53576 G/G infants who were not breastfeeding had higher depression scores as opposed to mothers of A/A infants ($P < .05$).
Krol 2019			x	Maternal/infant engagement in free play interaction	Structural equation modeling and multigroup path analysis	Maternal engagement at 5 months predicted a decrease in infant DNAm

(*continued on next page*)

Table 3 (*continued*)

Author, Year	Postnatal Outcome Category			Measures	Statistics	Major Findings
	Breast-feeding	*Maternal Mental Health*	*Maternal Caregiving Behavior*			
						over time. Maternal and infant *OXTR*m levels were positively correlated with each other to a similar extent at both visits at CpG −924 (*P=.004*).
Lee, 2019		x		Depression, Anxiety and Stress Scale (DASS-21)	Multiple regression	Among women with GDM, those with AA or AG genotypes of *OXTR* rs53576 were 3.0 times more likely to suffer from stress symptoms compared to those who carried GG genotype in the SNP (*P=.039*).No significant relationship with depression symptoms were found.
Lucas, 2021	x			Quantititave sensory tsting (QST) for baseline pain assessment; self-report pain nipple/breast pain at 1, 2, 6 wks. PP with pain scale	Kruskal-Wallis one-way analysis of variance on ranks, fisher exact, linear mixed modeling	Minor allele (A) *OXTR* rs53576 had a significant effect on breast and nipple pain severity over time (*P=.036*, 95% CI, .55–15.2). Women experienced an 8.18 increase in pain scores over time with the addition of one minor allele.
Mehta 2016		x	x	Adult Separation Anxiety (ASA) Scale, Maternal Separation Anxiety Scale (MSAS) Anxiety scale completed at an average of 30 weeks gestation and again at an average of 3 mo. PP	Linear & logistic regression for multivariate modeling	Based on rs53576, rs2254298, and rs1042778, mothers with a higher *OXTR* cumulative genetic risk score showed significantly decreased levels of observed maternal sensitivity as measured during free play and reunion episodes (*P=.038*) at 3 mo. PP. *OXTR* rs968389 was significantly associated with maternal oxytocin response (covariates age and ethnicity) *(P=.003)*.
Mileva-Seitz 2013		x	x	Ainsworth Maternal Sensitivity Scales, mother-infant interactions and responsiveness during recorded sessions, CES-D, CTQ, Parental Bonding Instrument (PBI), Life History Calendar (LHC)	ANOVA, models generated to test gene × environment interactions: multivariate regression models, F-test for model reduction, mediation models	Genotype associated with early care quality effects (for both rs2740210 and rs4813627) on maternal depression score (CES-D) at 6 months (*P < .001*). Mothers scored lower on depression as the early care quality increased, but the slopes for *OXT* genotypes C/C (rs2740210) and G/G (rs4813627) were more negative, indicating that early life experience had a stronger moderating effect in this group of mothers than in mothers with other genotypes. For *OXT* rs4813627 depression score decreased with increasing education (*P < .05*). There were no effects of OXTR genotype (rs237885) on depression levels at 6 months postpartum. However, a prenatal depression measure showed significant associations between *OXTR* rs237885 genotype G/G (*P=.003*).
Robakis 2020		x		Structured Clinical Interview for DSM-5 (SCID), *Attachment Style* Questionnaire (ASQ), EPDS, CTQ	Sliding-window based statistical analysis approach to identify differentially methylated regions	Methylation density at several sites was correlated either positively or negatively (± below) with perinatal depression (significant associations noted as *P < .05* or *P < .01* are bolded below) Total mean *OXTR*m not significantly associated with ante- or postnatal depression. Positions on chr3, hg 19, related to perinatal depression, cpg: 8806364 (+, ante); **8809167** (+, ante); 8809363 (+, ante); **8809463** (+, ante); **8809670** (-, ante); 8809699 (+, ante); 8809775 (+, ante); 8810062 (-, post); **8810067** (-, post); **8810076** (-, ante/post); 8810219 (+, post); **8810707** (-, ante/post);

(*continued on next page*)

Table 3 (*continued*)

Author, Year	Postnatal Outcome Category			Measures	Statistics	Major Findings
	Breast-feeding	*Maternal Mental Health*	*Maternal Caregiving Behavior*			
						8810873 (-, ante/post); **8811217** (-, ante/post); 8811241 (+, ante); **8811271** (+, ante) Of note: this study supported prior findings of a significant relationship between childhood maltreatment and *OXTR*m
Toepfer (1), 2019			x	Maternal intrusiveness during standardized play situation (NICHD Early Child Care Research Networt)	Linear mixed effects model and post-hoc analysis	DNAm of OXT-promotor region changed during pregnancy ($P < .001$). Mothers with more intrusive behaviors had 6% higher DNAm in late pregnancy ($P < .05$).
Toepfer (2), 2019			x	CTQ, Infant-Toddler *Home Observation for Measurement of the Environment (HOME-IT)*, Strange Situation Procedure	Linear mixed effects model and post-hoc analysis	No main effect of childhood maltreatment (CM) on maternal behavior ($P=.2$) were found; but there was a moderating effect by genotype. In women carrying the T-allele, CM-exposure correlated with more maternal insensitivity than non CM-exposure ($P=.015$). Infant attachment was higher in children of women with less maternal insensitivity ($P < .05$) for OXTR rs237895 (T-carrier vs C/C).
Unternaehrer 2016		x		EPDS, Inventory of Stressful Life-Events (ILE), socio-demographics, Trier Inventory for *Chronic Stress (TICS, short version)*	Linear mixed models and unstructured variance-covariance analysis	EPDS score ($P=.007$) was negatively associated with DNA methylation Of note: number of stressful life events and cortisol measures were also negatively correlated with methylation measures
Wiley, 2022		x		BDI, Beck Anxiety Inventory (BAI)	Spearman's rank correlation analyses, t-tests, mutilvariable regression models	Increased maternal anxiety symptoms in late pregnancy associated with lower infant DNAm at *OXTR2* CpG2 ($P=.3$) and increased infant evening cortisol ($P=.03$). *OXTR2* methylation was inversely related to evening cortisol ($P</.001$)

Table 4
OXTR/OXT SNP rs & outcome domain.

First Author, Year	Postnatal Outcome	*OXTR*[a]	*OXTR*[b]	*OXTR*[b]	*OXTR*[b]	*OXTR*	*OXTR*	*OXT*	*OXT*
		53576	1042778	2254298	237885	237895	968389	2740210	4813627
Asherin, 2020	MMH	x[c]							
Bhatti, 2019	MMH	x[c]							
Bell, 2015	MMH	x[c]		x					
Cao, 2021	MMH	x							
Dewell, 2018	MMH				x[c]				
Feldman, 2013	MB		x	x[c]					
Incollingo Rodriguez, 2022	MMH	x[c]							
Jonas, 2013	BF & MMH				x			x[c]	x
Julian, 2019	MB	x	x[c]						
Kimmel, 2016	MMH	x							
Kovacs, 2020	BF & MMH	x[c]							
Lee, 2019	MMH	x							
Lucas, 2022	BF	x[c]		x					
Mehta, 2016	MB	x[c]	x[c]	x[c]			x[c]		
Mileva-Seitz, 2013	MB & MMH				x[c]			x[c]	x[c]
Toepfer, 2019-2	MB					x[c]			

NOTE: Colodro-Conde excluded from this table assessed 19 *OXT* & 137 *OXTR* SNPs, highest hit was *OXTR* rs237899, top 20 hits listed in Table 3; Mehta SNPs used to calculate genetic risk included from total of 19 assessed SNPs.
Abbreviation code: Breastfeeding (BF), Maternal Caregiving Behavior (MB), Maternal Mental Health (MMH).
[a] Most commonly studied SNP.
[b] Second most commonly studied SNPs.
[c] Significant finding.

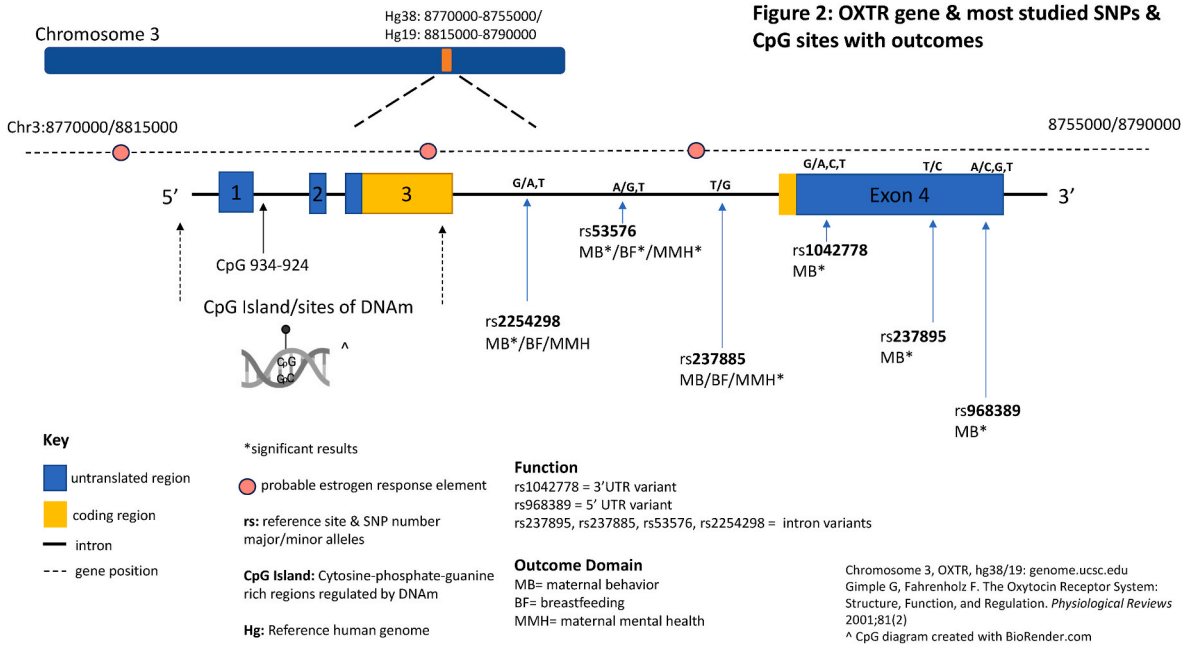


Fig. 2. OXTR gene & most studied SNPs & CpG sites with outcomes.

to report on maternal perceptions of nipple pain, which is one of the most commonly cited reasons for early breastfeeding cessation [68]. Variations at two *OXTR* SNPs were associated with increased perceived nipple pain during somatosensory testing within the first six postnatal weeks: A-carriers at rs53576 reported increased pain compared to GG counterparts. The same pattern held for rs2254298, with A-carriers reporting hypersensitivity to a "brush test" applied to the nipple. In summary, the findings suggest complex interactions exist involving OXT system genetic variation and early life adversity or maternal depression and breastfeeding exclusivity or duration [54,67], with some data suggesting nipple pain may be modulated by *OXTR* SNP variations [58].

3.2.3. *Maternal caregiving behavior*

Five out of six studies reported significant associations between *OXTR* SNPs and measures of maternal caregiving behavior [55,59,61,64,69]. Similar to the findings noted in the breastfeeding studies, these findings were seen as statistical interactions with adverse or stressful childhood experiences in three of the studies. One investigator assessed both *OXT* and *OXTR* SNPs, while the remaining four studies focused only on *OXTR* SNPs. Mileva-Seitz et al. found maternal-infant interactions were associated with *OXT* SNP genotypes rs2740210 and rs4813627, in that A-carriers were more impacted by early life care-giving experiences. Interestingly, the mother's early care quality, an index derived from several measures, interacted with genotype to impact current maternal care and postnatal depression, again highlighting a gene by environment role for quality of maternal caregiving behavior. The authors also found that the *OXTR* rs237885 (G allele) was associated with prenatal depression. The Feldman, Julian, Mehta, and the second Toepfer papers all noted significant interactions between allelic variation in different *OXTR* SNPs and maternal early life care experiences on current caregiving behavior quality or quantity [59,61,64,69] In summary, the majority of maternal caregiving behavior studies found a correlation between *OXTR* SNP variation and maternal caregiving behaviors including mother-infant interactions, maternal intrusiveness, and maternal sensitivity—though this association was moderated by the mothers' own early life experiences.

3.2.4. *Maternal mental health*

Maternal mental health variables included measures of psychosocial stress and/or postnatal depression or anxiety symptoms or diagnosis (Table 1). *OXTR* rs53576 was the most commonly studied SNP with eight studies reporting maternal mental health outcomes relative to this genotype (Table 4). The majority of this literature demonstrated that the G-allele carriers (GG homozygous or AG heterozygous) were at risk for depression or psychosocial stress experiences [53,56,70,71]. In contrast, Lee et al. found carrying the A allele more highly associated with maternal depression or stress, and Cao et al. found no associations between variations in rs53576 and mental health outcomes, even when childhood maltreatment interactions were included. However, when examining infants' genotypes, Asherin et al. found that mothers of GG (rs53576) infants were more likely to have elevated depression symptoms. Although GG mothers were more likely to have higher depression scores independently, this interaction did not hold when controlling for infant genotype and demographic factors, and only infant genotype was significantly predictive [56]. Lastly, the recent publication by Incolingo-Rodriguez et al. assessed rs53576, and, like the Bell et al. study discussed later, found the G carriers to be more likely to have elevated symptoms of postnatal depression and anxiety when exposed to prenatal stressors (characterized as discrimination and acculturation) than their AA counterparts [71].

Focusing on another SNP, Dewell et al. found a relationship between psychosocial stress and allelic variation at *OXTR* rs237885, as homozygous GG mothers were less likely to be in the high social stress group [72]. This SNP was also studied by Mileva-Seitz et al., and GG was linked significantly lower prenatal depression [69]. Together, these studies support a relationship between OXT system genetic variation and maternal depression and infant interactions, likely dependent on other social contexts. The Asherin and Kovacs papers both initially found higher depression scores in mother of GG *infants*, suggesting a possible emotional reciprocity in the mother-infant relationship influenced by genotype.

3.3. *DNAm studies*

DNA methylation is generally assessed via epigenome-wide association (EWAS) or targeted methylation (loci-specific) methods [73]. In the former, methylation density is quantified across the genome, and researchers can observe overall patterns of increased or decreased methylation in various sites/genes. Loci-specific studies assess methylation density at a particular CpG site or sites, ideally determined *a-priori*.

The methylation studies included here are all loci-specific. Another important feature of the DNAm studies were the examination of infant DNAm markers, as well as maternal DNAm. We present findings related to maternal caregiving behavior and mental health only, as no studies related breastfeeding outcomes to DNAm in either infants or mothers.

3.3.1. Maternal caregiving behavior

Only two studies reported on DNAm and maternal caregiving behavior. Krol et al. reported that maternal and infant methylation patterns were positively correlated with each other, and that higher maternal engagement predicted a decrease in infant *OXTR* methylation over time at CpG site −924 [62]. Toepfer et al. described a significant relationship between methylation at an *OXT* promotor region CpG site (cg16887334) and maternal caregiving behavior in the postnatal period. Specifically, the authors assessed for maternal intrusiveness, described as behaviors that are incongruent with infant cues for rest or disengagement and associated with maternal anxiety [63]. They found that mothers with increased DNAm at this site in late pregnancy had increased maternal intrusiveness at 6 postnatal months, and that the methylation profile generally decreased from early to mid-pregnancy.

3.3.2. Maternal mental health

Six authors examined *OXTR* methylation patterns of mothers or infants in relationship to prenatal and postnatal depression or depression symptoms. Robakis et al. noted increased maternal *OXTR* methylation density at numerous sites related to perinatal depression, childhood trauma history, and insecure attachment style using buccal swabs. Kimmel et al., merging data from three cohorts, found a relationship between lower rates of *OXTR* DNAm (chr3: 8810078 & 8810069) and higher risk for postnatal depression among those *with* depression during pregnancy only [70]. Unternaehrer et al. found that the number of maternal adverse experiences in the two years preceding the second trimester of pregnancy along with maternal depression symptoms predicted reduced *OXTR* DNAm in newborn cord blood (chr3: 8809275–8809534). In the study by Galbally et al., *OXTR* DNAm was related to treatment of depressive symptoms; overall, placental *OXTR* DNAm was lower when the pregnant participant took antidepressant medication during pregnancy compared to individuals without depression symptoms or with depression symptoms but not taking antidepressants (Chr3: 8810680–8810890). Among participants taking antidepressants, and controlling for third trimester symptoms, methylation in infant cord blood was higher in samples with greater measured concentrations of SSRI medication. Incollingo-Rodriguez et al. noted that only in the lowest tertile of *OXTR* DNAm (−934), prenatal acculturation predicted postnatal depression. The newest study included in this review by Wiley et al., found that *OXTR* DNAm was lower in infants of mothers reporting higher anxiety and that higher levels of infant cortisol were inversely related to *OXTR* DNAm at certain sites labeled in the paper as OXTR1 (8808467–8810658) and OXTR2 (8808058–8810304) [65]. Importantly in these studies, directionality of the relationship between maternal or infant DNAm density and maternal depression or anxiety symptoms was dependent on CpG site and tissue type [65,74–76].

3.4. SNP and DNAm interaction study

Given that an individual's OXT system can vary by DNAm density and genetic sequence, examining the interaction of these two variables may lead to a more robust understanding of outcomes. One study evaluated this interaction statistically [53].

3.4.1. Maternal mental health

Bell et al. found that neither allelic variation at *OXTR* rs53576, nor methylation status alone predicted postnatal depression. Rather, women (without prenatal depression) who possessed a GG genotype and had higher *OXTR* DNAm (site −934) had greater odds for postnatal depression compared to A-carriers. Interestingly, while the *OXTR* methylation findings by Incollingo-Rodriguez et al. and Kimmel et al. show an opposite relationship between methylation and postnatal depression when compared to the earlier study conducted by Bell et al., the Bell study did note a non-significant association between lower rates of *OXTR* methylation and postnatal depression in GG genotype carriers with prenatal depression. Even so, these seemingly contradictory findings may support the contextual variability of the OXT system and subsequent adaptive measures.

This interaction study highlights the important possibility that more complex relationships drive epigenetic and SNP differences as well as the role of critical social experiences (e.g., childhood trauma, discrimination or acculturation) in the development of poor postnatal mental health. These data suggest that an *OXTR* G "risk allele" represents an increased sensitivity to environmental stimuli, both positive and negative. Implications will be further addressed in the discussion.

4. Discussion

4.1. Key findings

In this scoping review we present the extant literature on genetic and epigenetic variation within the human oxytocin system related to breastfeeding, maternal caregiving behavior, and maternal mental health. Of these outcome domains, maternal mental health was most frequently studied. Many papers included evaluation of the additive effect of *OXTR* genotypes with environmental exposures (adversity or stress) in relation to suboptimal mood or behavioral outcomes. Few studies examined breastfeeding specifically. Studies that reported the relationship between maternal engagement and infant DNA methylation suggest that maternal caregiving impacts early methylation patterns, which has been robustly demonstrated in the animal literature [43].

4.2. Gene × environment interactions: in sum

The complexity of the OXT system and its relationship with environmental factors is most powerfully highlighted by studies investigating gene and environment interactions. Ten studies in this review included such findings [22,59,63,65,67,70,71,74,75,77], and only Cao et al. reported no significant relationships. Childhood trauma, maltreatment, or other adverse early life experiences either interacted with genotype to impact maternal postnatal outcomes [59,64,67], or were associated with variations in *OXTR* methylation profiles [70,75]. In one instance, social support and genotype buffered current stress experiences [22], and in two other studies maternal depression symptoms or perinatal stress experiences were associated with decreased maternal or infant *OXTR* DNAm [65,74]. Taken together, the findings in these human studies support what we know from animal models [43]: plasticity in early development allows a window of impact for both positive and negative exposures. However, the impact of such exposures may vary by an individual's genotype (Fig. 3).

These data support the study of nurture-focused social interventions on influencing long-term function of the OXT system. Interventions focused on resilience, support, and equity have potential to capitalize on this relationship between lived social experiences and candidate OXT-mediated health outcomes. For example, interventions that target culturally relevant social support during pregnancy may mitigate experiences of social stress.

4.3. Genetic variation indicates vulnerabilities to stress in the development of maternal mental health disorders

OXTR variant rs53576 was the most studied *OXTR* SNP in this review. Several published reviews suggest that the G allele of rs53576 is highly associated with sensitivity to social stimuli (i.e. empathy) or greater responsiveness to social experiences [78,79]. Conversely, the A

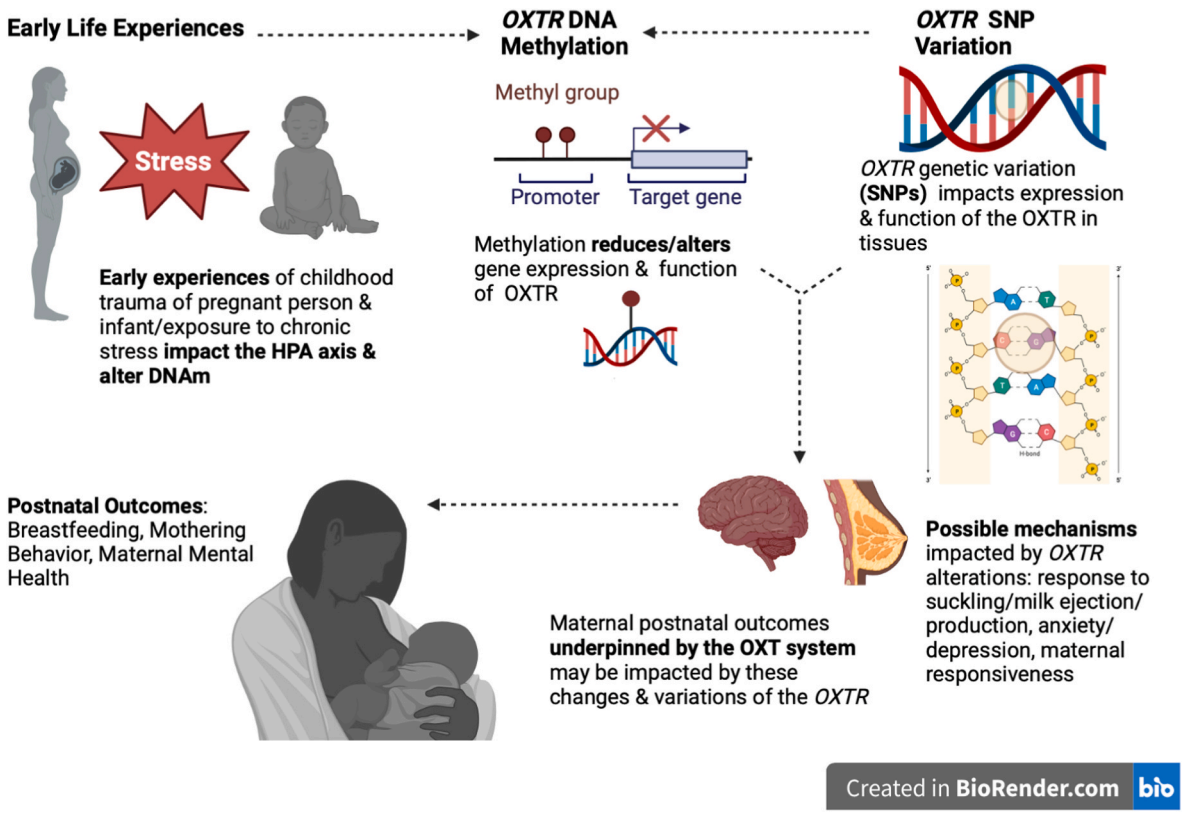


Fig. 3. Conceptual model depicting relationships between early life experiences, genetic and epigenetic variation of *OXTR*, and postnatal outcomes.

allele of rs53576 has generally been associated with reduced sensitivity to environmental or social stimuli and less prosocial behavior [24]. This may indicate that the G allele provides increased sensitivity to environmental stimuli, meaning that both positive and negative input may have a greater impact on the individual, which is in line with existing theory on gene by environment interactions [80]. Literature in this review supports this hypothesis, suggesting that the G allele of rs53576 is associated with higher risk for depression or anxiety [53,56,71]. For instance, G carriers may be more sensitive to both positive and negative social stimuli and may therefore have higher rates of depression, particularly when exposed to stressful experiences. On the other hand, G carriers without stressful exposures were not at increased risk for adverse mood or mothering behaviors, indicating that genetics are important but not deterministic in mothering and mental health manifestations. Similarly, early life exposures or stressors *alone* were not deterministic in predicting greater maternal depression symptoms in these studies.

4.4. Epigenetic variation & genetic interaction May indicate compensatory or adaptive mechanisms

Levels of DNA methylation of OXT system genes in the context of stressful experiences can be interpreted in a variety of ways including: 1) demethylation (or blocking methylation via hydroxymethylation) is a compensatory mechanism which occurs during or following stressful situations, thereby allowing for more OXT signaling, or 2) increased methylation occurs as an adaptive mechanism useful in dampening OXT responses (indicating a chronically over-activated stress response) [49, 81].

In the context of this review, lower DNA methylation may be occurring as a compensatory response to depression [9]. In contrast, when researchers note increased methylation density in relationship to reduced maternal caregiving behavior or poor mental health outcomes, this may reflect an adaptive dampening of OXT sensitivity in response to chronic social stress or early trauma. This is supported by the impact of early care on the epigenome [43], and the involvement of the OXT system in danger discernment and adaptive versus maladaptive responses [3,82,83]. Among the reviewed studies that assessed DNAm, density was related to stress, early life experiences, or depression; however, directionality depended upon the SNP and/or social context (e.g., support or early life experiences). Maternal genotype and site-specific methylation variability may interact to impact experiences of, and responses to, environmental stress resulting in potential mental health changes, as discussed in the study by Bell et al.

In the paper by Galbally et al., the correlation of higher serum level of antidepressant medication with higher infant cord blood methylation may be linked to non-specific assay methods (detection of hydroxymethylation) or reflect differences in placental versus fetal responses to maternal medication use [76]. The findings in the Galbally paper also align with those in the Unternaehrer and Robakis studies, and may be interpreted using a predictive adaptive response model characterized by Gluckman et al. With this application, higher levels of infant methylation could indicate reduced compensatory mechanisms (demethylation) due to reduced perinatal stress experiences (fewer stressful events or medically treated depression) [81]. Maternal stress experiences have been associated with blunted infant stress responses, operationalized as cortisol-reactivity, which supports this potential in-utero adaptive mechanism [84,85]. This interpretation and theoretical assessment signals an important area of further research: descriptions of methylation status in neonates, upstream predictors, and downstream implications for development.

4.5. Breastfeeding & lactation: a primary early life dyadic experience chronically absent in the literature

Despite animal and human literature linking OXT to breastfeeding and lactation, few studies have evaluated if *OXT* or *OXTR* genetic and epigenetic variation is associated with breastfeeding outcomes. Of the

limited studies, our review findings support a hypothesis that the OXT system has complex interactions with various environmental exposures which should be studied further in the context of lactation [54,67]. This hypothesis is also supported by the general finding that maternal depression and other social experiential factors are negatively associated with breastfeeding outcomes [86,87]. However, biomarkers which may predict poor lactation-related outcomes linked with *OXT/OXTR* have yet to be investigated. Both nipple pain and "not enough milk" are two of the most commonly cited reasons for formula supplementation [68]. OXT plays an important role in pain and stress modulation [9, 88–90] thus another important avenue for exploration is genetic (or epigenetic) moderation of pain sensitivity or perception, as was the focus of Lucas et al. [58] Especially compelling is the possibility that *OXTR* rs53576 could be associated with both physical and social-emotional sensitivity related to OXT system regulation. The foundational involvement of the OXT system in both the physiologic and psychosocial aspects of the mother-infant breastfeeding relationship warrants future research.

4.6. Clinical relevance and future directions

Perinatal care providers typically do not receive training on the complexity of the behavioral neuroscience governing the OXT system, or are unfamiliar with the research showing the role of OXT in pre and postnatal experiences. Yet, ideal obstetric or mental health care accounts for individual context and lived experiences. Therefore, care may be most effective when considering the intersection of the environment and biological responses that are sensitive to the environment [91,92]. Knowledge that depression or parenting behaviors may be influenced by both prior stressor and genetic vulnerability provides clues into the various postnatal experiences providers witness in their clientele. Further, understanding the potential for maternal depression to alter the infant's *OXTR* DNAm underscores the importance of the infant's environment and family health. Recognition of the genetic and epigenetic variation in general OXT function (and those specifically linked to perinatal outcomes) can be appreciated as basic research and shared by clinicians as such.

Lastly, in the era of precision medicine, treatments are currently being tested and tailored to individual SNP profiles in cancer therapy, mental health treatment, and hypertension [93–95]. Future research on genetic and epigenetic variation in the OXT system, including CD38, may provide opportunities to tailor the effectiveness of therapies in improving maternal caregiving behavior, perinatal depression or breastfeeding outcomes. Research on the potential genetic underpinnings of functional complications of breastfeeding (e.g., dysphoric milk ejection reflex, pain, and insufficient milk supply) would greatly benefit parents who struggle to find answers or treatments to meet breastfeeding goals. Research is also needed to determine how methylation and SNPs interact in relationship to breastfeeding, and also likely to other loci of interest that have emerged in the literature (e.g., with metabolic implications) [48,96–102].

4.7. Theoretical models for understanding complex neurobehavioral processes: importance & limitations

OXT-dependent social and reproductive processes are complex and require multi-layered frameworks, such as the extensively conceptualized Developmental Origins of Health and Disease (DOHD) [103]. For example, maternal early life experiences interact with maternal genotype to generate epigenetic changes in stress response; this in turn impacts maternal caregiving behavior and the offspring's in-womb biochemical environment and subsequent early life experiences [49]. This intergenerational framework provides an overlay of social and physiologic mechanisms that impact human reproduction and development. While the development of biomarkers indicating vulnerability (or resilience) to social stress lags behind our theoretical understanding of these mechanisms, this field is growing and offers promising avenues for operationalizing these concepts [104].

Human psychobiology and physiology can be described as a product of the complex interplay between genetic material and epigenetic markers within the experienced environment [42]. Epigenetic research may be an avenue by which we can better understand the plasticity of the developmental continuum: how and when environmental impacts can alter our physiology, and subsequent physical and psychological health outcomes. When appropriately placed in the context of environment, understanding of the impact of transgenerational experiences on health may be better understood. Perhaps positive environmental changes can impact physiology and support healing and resilience. Social interventions targeted at maternal-child health may have the ability to embed positive change in our biology and psychology, which is yet another compelling reason to follow this line of research. Finally, the OXT system is intimately involved with the stress response [9]. This relationship provides scaffolding for the argument that there may be a bi-directional relationship between the OXT and stress systems, and that prolonged stress exposure may well alter OXT system functioning. Epigenetics offers one potential mechanism for this phenomenon, and has the potential to be supported by other bio-embedding frameworks such as allostatic load [105]. Future and ongoing research in this area should include operationalized social determinants of health such as experienced racism, neighborhood characteristics, access to resources, etc.

4.8. Limitations

The included studies had several key limitations inherent in many genetic and epigenetic studies. The review's perinatal outcomes represent social, behavioral, and physiologic phenomenon that would benefit from complex modeling to capture genetic, epigenetic, and environmental interaction. Any literature with an epigenetic component should consider upstream contributions towards such epigenetic alterations such that the biopsychosocial context is not lost from the dialogue. While a subset of our studies included information on social determinants of health (e.g., trauma history), many did not. The heterogeneity of available studies was significant and made consolidation of conclusions challenging. For example, while certain SNPs were studied more frequently than others (e.g., rs53576) a range of SNPs were assessed across studies. Likewise, methylation sites ranged from regions to specific CpG sites. Additionally, studies varied in their operational measures and definitions of depression, anxiety, psychosocial stress, and mothering behaviors. Studies that utilized older retrospective data may be limited by changing societal norms, for example, the study by Colodro-Conde et al. (2018) utilized data from time periods when formula feeding was very normative.

Assessment of DNA methylation varied in ways that may also contribute to potential heterogeneity of results. For example, some studies collected buccal samples while others utilized blood samples, which may not be comparable as methylation can vary by tissue type. The timing of sample collection may also impact findings such that methylation during pregnancy may not be static and may also differ from postnatal methylation patterns.

Studies with genetic components inherently are impacted by geographic ancestry of the participants. The majority of participants were of European ancestry, and some studies used terms such as "Caucasian" or "[not] a minority," which are considered outdated and nonspecific [33,106]. In some cases, ancestry/ethnicity was not available, which can also have implications for erasure of experiences that might impact psychosocial and methylation measures [106]. While common ancestry may be helpful in terms of limiting variation in population allele frequency, most genetic research to-date has been conducted within populations originating in European countries [107]. This limitation is especially important in social stress and social determinants research as historical trauma, oppression, and experiences of racism and discrimination impact physiology via biological embedding [34].

Another reason diverse representation in genetic research is necessary is due to allelic variation of certain SNPs (e.g. rs53576 *OXTR*) between ancestral populations [108]. In this example, the minor genotype differs in Asian-ancestral populations compared to other populations (GG is present in a minority of the population whereas AA is seen less commonly in European and African populations). Thus, if a study concludes that "AA" homozygotes had a higher risk of postnatal depression, but only samples European-ancestral groups, the study and genotype-association may not be generalizable without adequate representation in other populations. A minor allele in one population may not be a minor allele in a second population limiting the generalizability of genotypic results.

This scoping review was limited by several factors. The potential for reviewer bias was present but minimized in two ways. While each screening and full-text review was conducted by two authors, data abstraction was conducted by individual reviewers with issues resolved by group consensus. While two of the reviewers co-authored an article cited as background material, and one of the reviewers was first author of an article included in the final scoping results, we assigned non-contributing coauthors to screen, review and abstract data. Scoping reviews do not generally assess the quality of evidence, thus we did not engage in a formal assessment of the strength of evidence.

5. Conclusion

The results of this scoping review demonstrate the complexity of the OXT system. While the role of the OXT system in a range of perinatal outcomes is well established, the implications of allelic variation and DNA methylation have been challenging to ascertain. The literature at large remains most robust around psychopathologic outcomes, and this was born out in our review of the maternal mental health outcomes. The data suggest that there is an interaction between postnatal depression, *OXTR* genotype, and *OXTR* methylation; however, the context for these outcomes is complicated and requires further study. The importance of early life and social experiences on OXT system function was a recurrent theme, and deserves further mechanistic investigation. Future research should incorporate complex modeling, social context, and stress systems in order to provide insight into mechanisms underlying perinatal health outcomes in relationship to the oxytocin system.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Note on gendered language and inclusivity

The use of the words "mother," "maternal," or "woman," and their derivatives are recognized by the authors as gendered and not preferred terminology to promote inclusivity in research. They are used here to reflect the language in the studies meeting inclusion criteria for this review and for consistency. The findings noted here are intended to apply to any lactating or birthing parent in the postnatal period.

Author contributions

Sarah R. Weinstein: Conceptualization, Data Curation, Writing, Review & Editing, Visualization, Project Administration **Elise N. Erickson:** Conceptualization, Data Curation, Writing, Review & Editing, Visualization, Supervision **Rodin Molina:** Conceptualization, Data Curation, Visualization **Aleeca F. Bell:** Conceptualization, Data Curation, Writing, Review & Editing, Visualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors would like to thank health sciences librarian, Maribeth Slebodnik, RN, MS, for her guidance and support of this project.

References

[1] C.S. Carter, The role of oxytocin and vasopressin in attachment, Psychodyn. Psychiatry (2017) 499–518.
[2] B.N. Jurek, D. Inga, The oxytocin receptor: from Intracellular signaling to behavior, Physiol. Rev. 98 (3) (2018), https://doi.org/10.1152/physrev.00031.2017.
[3] D.S. Quintana, A.J. Guastella, An allostatic theory of oxytocin, Trends Cogn Sci. 24 (7) (2020) 515–528, https://doi.org/10.1016/j.tics.2020.03.008. Jul.
[4] T. Li, P. Wang, S.C. Wang, Y.F. Wang, Approaches mediating oxytocin regulation of the immune system, Front. Immunol. 7 (2016) 693, https://doi.org/10.3389/fimmu.2016.00693.
[5] C.S. Carter, Oxytocin and love: Myths, metaphors and mysteries, Comprehensive Psychoneuroendocrinology 9 (2022), https://doi.org/10.1016/j.cpnec.2021.100107.
[6] C.S. Carter, Oxytocin pathways and the evolution of human behavior, Annu. Rev. Psychol. (2014) 17–39.
[7] R. Feldman, M. Monakhov, M. Pratt, R.P. Ebstein, Oxytocin pathway genes: evolutionary Ancient system impacting on human affiliation, sociality, and psychopathology, Biol Psychiatry: Elsevier (2016) 174–184.
[8] B. Jurek, D.A. Slattery, Y. Hiraoka, et al., Oxytocin Regulates stress-induced Crf gene transcription through CREB-Regulated transcription Coactivator 3, J. Neurosci. 35 (35) (2015) 12248–12260, https://doi.org/10.1523/JNEUROSCI.1345-14.2015. Sep. 2.
[9] J. Winter, B. Jurek, The interplay between oxytocin and the CRF system: regulation of the stress response, Cell Tissue Res. 375 (1) (2019) 85–91, https://doi.org/10.1007/s00441-018-2866-2. Jan.
[10] A.F. Bell, E.N. Erickson, C.S. Carter, Beyond labor: the role of natural and synthetic oxytocin in the transition to motherhood, J. Midwifery Wom. Health (2014) 35–42.
[11] R. Feldman, Oxytocin and social affiliation in humans, Horm. Behav. (2012) 380–391.
[12] R. Feldman, The Neurobiology of Human Attachments, Trends Cogn Sci: Elsevier Ltd, 2017, pp. 80–99.
[13] R. Feldman, M.J. Bakermans-Kranenburg, Oxytocin: a parenting hormone, Current Opinion in Psychology: Elsevier (2017) 13–18.
[14] P. Kim, R. Feldman, L.C. Mayes, et al., Breastfeeding, brain activation to own infant cry, and maternal sensitivity, J Child Psychol Psychiatry (2011) 907–915.
[15] M. Khajehei, Labour and beyond: the roles of synthetic and endogenous oxytocin in transition to motherhood, Br. J. Midwifery (2017) 230–238.
[16] K. Pierzynowska, L. Gaffke, M. Zabinska, et al., Roles of the oxytocin receptor (OXTR) in human diseases, Int. J. Mol. Sci. 24 (4) (2023), https://doi.org/10.3390/ijms24043887. Feb 15.
[17] D.S. Quintana, J. Rokicki, D. van der Meer, et al., Oxytocin pathway gene networks in the human brain, Nat. Commun. 10 (1) (2019) 668, https://doi.org/10.1038/s41467-019-08503-8. Feb 8.
[18] O. Lopatina, A. Inzhutova, A.B. Salmina, H. Higashida, The roles of oxytocin and CD38 in social or parental behaviors, Front. Neurosci. 6 (2012) 182, https://doi.org/10.3389/fnins.2012.00182.
[19] K.A. Hogan, C.C.S. Chini, E.N. Chini, The multi-faceted ecto-enzyme CD38: roles in immunomodulation, cancer, aging, and metabolic diseases, Front. Immunol. 10 (2019) 1187, https://doi.org/10.3389/fimmu.2019.01187.
[20] J.S. Danoff, K.L. Wroblewski, A.J. Graves, et al., Genetic, epigenetic, and environmental factors controlling oxytocin receptor gene expression, Clin Epigenetics. 13 (1) (2021) 23, https://doi.org/10.1186/s13148-021-01017-5. Jan 30.
[21] M.J. Bakermans-Kranenburg, M.H. van Ijzendoorn, A sociability gene? Meta-analysis of oxytocin receptor genotype effects in humans, Psychiatr. Genet. 24 (2) (2014) 45–51, https://doi.org/10.1097/YPG.0b013e3283643684. Apr.
[22] P. Bhatti, T. Delaney, M. Poulin, J. Hahn-Holbrook, Oxytocin receptor gene (OXTR) and father support interact to predict depressive symptoms postpartum, Biol. Psychol. 147 (2019), 107686, https://doi.org/10.1016/j.biopsycho.2019.03.015. Oct.
[23] N.R. Bush, A.L. Allison, A.L. Miller, J. Deardorff, N.E. Adler, W.T. Boyce, Socioeconomic disparities in childhood obesity risk: association with an oxytocin receptor polymorphism, JAMA Pediatr. (2017) 61–67.
[24] D. Choi, K.J. Tsuchiya, N. Takei, Interaction effect of oxytocin receptor (OXTR) rs53576 genotype and maternal postpartum depression on child behavioural problems, Sci. Rep. 9 (1) (2019) 7685, https://doi.org/10.1038/s41598-019-44175-6. May 22.
[25] N.C. Ebner, T. Lin, M. Muradoglu, et al., Associations between oxytocin receptor gene (OXTR) methylation, plasma oxytocin, and attachment across adulthood, Int. J. Psychophysiol. (2019) 22–32.

[26] C.I. Park, H.W. Kim, S. Jeon, J.I. Kang, S.J. Kim, Reduced DNA methylation of the oxytocin receptor gene is associated with obsessive-compulsive disorder, Clin Epigenetics (2020) 1–9.
[27] A.M. Perkeybile, C.S. Carter, K.L. Wroblewski, et al., Early nurture epigenetically tunes the oxytocin receptor, Psychoneuroendocrinology: Elsevier (2019) 128–136.
[28] H.E. Poore, I.D. Waldman, The association of oxytocin receptor gene (OXTR) polymorphisms with Antisocial behavior: a meta-analysis, Behav. Genet. 50 (3) (2020) 161–173, https://doi.org/10.1007/s10519-020-09996-6. May.
[29] L. Ramo-Fernandez, A.M. Gumpp, C. Boeck, et al., Associations between childhood maltreatment and DNA methylation of the oxytocin receptor gene in immune cells of mother-newborn dyads, Transl. Psychiatry 11 (1) (2021) 449, https://doi.org/10.1038/s41398-021-01546-w. Sep. 1.
[30] C. Maud, J. Ryan, J.E. McIntosh, C.A. Olsson, The role of oxytocin receptor gene (OXTR) DNA methylation (DNAm) in human social and emotional functioning: a systematic narrative review, BMC Psychiatr.: BMC Psychiatr. (2018) 1–13.
[31] S. Li, T.O. Tollefsbol, DNA methylation methods: Global DNA methylation and methylomic analyses, Methods. 187 (2021) 28–43, https://doi.org/10.1016/j.ymeth.2020.10.002. Mar.
[32] S.G. Gregory, J.J. Connelly, A.J. Towers, et al., Genomic and epigenetic evidence for oxytocin receptor deficiency in autism, BMC Med. 7 (2009) 62, https://doi.org/10.1186/1741-7015-7-62. Oct 22.
[33] M.K. Cho, M.L. Duque Lasio, I. Amarillo, K.T. Mintz, R.L. Bennett, K.B. Brothers, Words matter: the language of difference in human genetics, Genet. Med. 25 (3) (2023), 100343, https://doi.org/10.1016/j.gim.2022.11.011. Mar.
[34] P. Vineis, C. Delpierre, R. Castagné, et al., Health inequalities: embodied evidence across biological layers, Soc. Sci. Med.: Elsevier (2020), 112781.
[35] D. Roberts, Fatal Invention: How Science, Politics, and Big Business Recreate Race in the Twenty-First Century, The New Press, 2011.
[36] E.L. Smearman, L.M. Almli, K.N. Conneely, et al., Oxytocin receptor genetic and epigenetic variations: association with child abuse and adult psychiatric symptoms, Child Dev. (2016) 122–134.
[37] N.R. Bush, R.D. Edgar, M. Park, et al., The biological embedding of early-life socioeconomic status and family adversity in children's genome-wide DNA methylation, Epigenomics (2018) 1445–1461.
[38] V.B. de Mendoza, Y. Huang, C.A. Crusto, Y.V. Sun, J.Y. Taylor, Perceived racial discrimination and DNA methylation among African American women in the InterGEN study, Biol. Res. Nurs. (2018) 145–152.
[39] M. Rajaprakash, L.T. Dean, M. Palmore, et al., DNA methylation signatures as biomarkers of socioeconomic position, Environ Epigenet 9 (1) (2023) dvac027, https://doi.org/10.1093/eep/dvac027.
[40] S.S. Cobbinah, J. Lewis, Racism & Health: a public health perspective on racial discrimination, J. Eval. Clin. Pract. (2018) 995–998.
[41] Y. Paradies, J. Ben, N. Denson, et al., Racism as a determinant of health: a systematic review and meta-analysis, PLoS One (2015) 1–49.
[42] C. Pinel, B. Prainsack, C. McKevitt, Markers as mediators: a review and synthesis of epigenetics literature, BioSocieties (2018) 276–303.
[43] I.C.G. Weaver, N. Cervoni, F.A. Champagne, et al., Epigenetic programming by maternal behavior, Nat. Neurosci. (2004) 847–854.
[44] F.A. Champagne, J.P. Curley, Epigenetic mechanisms mediating the long-term effects of maternal care on development, Neurosci. Biobehav. Rev. (2009) 593–600.
[45] E.W. Fish, D. Shahrokh, R. Bagot, et al., Epigenetic programming of stress responses through variations in maternal care, Ann. N. Y. Acad. Sci. (2004) 167–180.
[46] C. Fontana, F. Marasca, L. Provitera, et al., Early maternal care restores LINE-1 methylation and enhances neurodevelopment in preterm infants, BMC Med. 19 (1) (2021) 42, https://doi.org/10.1186/s12916-020-01896-0. Feb 5.
[47] E. Garg, L. Chen, T.T.T. Nguyen, et al., The early care environment and DNA methylome variation in childhood, Dev. Psychopathol. (2018) 891–903.
[48] B.M. Lester, E. Conradt, L.L. LaGasse, E.Z. Tronick, J.F. Padbury, C.J. Marsit, Epigenetic programming by maternal behavior in the human infant, Pediatrics 142 (4) (2018), https://doi.org/10.1542/peds.2017-1890.
[49] P. Toepfer, C. Heim, S. Entringer, E. Binder, P. Wadhwa, C. Buss, Oxytocin pathways in the intergenerational transmission of maternal early life stress, Neurosci. Biobehav. Rev.: Elsevier (2017) 293–308.
[50] R.A.S. Alyamani, C. Murgatroyd, Epigenetic programming by early-life stress, Prog Mol Biol Transl Sci (2018) 133–150, chap. 7.
[51] M. Szyf, The epigenetics of perinatal stress, Dialogues Clin. Neurosci. 21 (4) (2019) 369–378, https://doi.org/10.31887/DCNS.2019.21.4/mszyf. Dec.
[52] R. Feldman, The neurobiology of mammalian parenting and the biosocial context of human caregiving, Horm. Behav.: Elsevier (2016) 3–17.
[53] A.F. Bell, C.S. Carter, C.D. Steer, et al., Interaction between oxytocin receptor DNA methylation and genotype is associated with risk of postpartum depression in women without depression in pregnancy, Front. Genet. 6 (2015) 243, https://doi.org/10.3389/fgene.2015.00243.
[54] R.P. Kovacs, Potential Moderating Role of Breastfeeding in the Relationship between Infant's Oxytocin Receptor (OXTR) Genotype and Postpartum Depression, University of Colorado at Denver, 2020.
[55] D. Mehta, V. Eapen, J. Kohlhoff, et al., Genetic regulation of maternal oxytocin response and its influences on maternal behavior, Neural Plast. 2016 (2016), 5740365, https://doi.org/10.1155/2016/5740365.
[56] R.M. Asherin, K.D. Everhart, S.L. Stophaeros, et al., Associations between maternal depression and mother and infant oxytocin receptor gene (OXTR_ rs53576) polymorphisms, Dev. Psychobiol. 62 (4) (2020) 496–504, https://doi.org/10.1002/dev.21938. May.
[57] L. Colodro-Conde, J.F. Sanchez-Romera, P.A. Lind, et al., No evidence of association of oxytocin polymorphisms with breastfeeding in 2 independent samples, Genes Brain Behav 17 (7) (2018), e12464, https://doi.org/10.1111/gbb.12464. Sep.
[58] R. Lucas, Y. Zhang, S.J. Walsh, A. Starkweather, E. Young, OXTR rs53576 variation with breast and nipple pain in breastfeeding women. Article, Pain Manag. Nurs. 22 (3) (2021) 369–376, https://doi.org/10.1016/j.pmn.2020.09.007.
[59] M.M. Julian, A.P. King, E.L. Bocknek, et al., Associations between oxytocin receptor gene (OXTR) polymorphisms, childhood trauma, and parenting behavior, Dev. Psychol. 55 (10) (2019) 2135–2146, https://doi.org/10.1037/dev0000783. Oct.
[60] K.W. Lee, S.M. Ching, V. Ramachandran, et al., Association analysis of 14 candidate gene polymorphism with depression and stress among Gestational Diabetes Mellitus, Genes 10 (12) (2019), https://doi.org/10.3390/genes10120988. Nov 30.
[61] R. Feldman, I. Gordon, M. Influs, T. Gutbir, R.P. Ebstein, Parental oxytocin and early caregiving jointly shape children's oxytocin response and social reciprocity, Neuropsychopharmacology: Nature Publishing Group (2013) 1154–1162.
[62] K.M. Krol, R.G. Moulder, T.S. Lillard, T. Grossmann, J.J. Connelly, Epigenetic dynamics in infancy and the impact of maternal engagement, Sci. Adv. 5 (10) (2019), eaay0680, https://doi.org/10.1126/sciadv.aay0680. Oct.
[63] P. Toepfer, K.J. O'Donnell, S. Entringer, et al., Dynamic DNA methylation changes in the maternal oxytocin gene locus (OXT) during pregnancy predict postpartum maternal intrusiveness, Psychoneuroendocrinology: Elsevier (2019) 156–162.
[64] P. Toepfer, K.J. O'Donnell, S. Entringer, et al., A role of oxytocin receptor gene brain tissue expression Quantitative Trait locus rs237895 in the intergenerational transmission of the effects of maternal childhood maltreatment, J. Am. Acad. Child Adolesc. Psychiatry 58 (12) (2019) 1207–1216, https://doi.org/10.1016/j.jaac.2019.03.006. Dec.
[65] K.S. Wiley, C. Camilo, G. Gouveia, et al., Maternal distress, DNA methylation, and fetal programing of stress physiology in Brazilian mother-infant pairs, Dev. Psychobiol. 65 (1) (2023), e22352, https://doi.org/10.1002/dev.22352. Jan.
[66] D.N. Cooper, Functional intronic polymorphisms: Buried treasure awaiting discovery within our genes, Hum. Genom. 4 (5) (2010) 284–288.
[67] W. Jonas, V. Mileva-Seitz, A.W. Girard, et al., Genetic variation in oxytocin rs2740210 and early adversity associated with postpartum depression and breastfeeding duration, Genes Brain Behav 12 (7) (2013) 681–694, https://doi.org/10.1111/gbb.12069. Oct.
[68] M.L. Gianni, M.E. Bettinelli, P. Manfra, et al., Breastfeeding Difficulties and risk for early breastfeeding cessation, Nutrients 11 (10) (2019), https://doi.org/10.3390/nu11102266. Sep. 20.
[69] V. Mileva-Seitz, M. Steiner, L. Atkinson, et al., Interaction between oxytocin genotypes and early experience predicts quality of mothering and postpartum mood, PLoS One 8 (4) (2013), e61443, https://doi.org/10.1371/journal.pone.0061443.
[70] M. Kimmel, M. Clive, F. Gispen, et al., Oxytocin receptor DNA methylation in postpartum depression, Psychoneuroendocrinology 69 (2016) 150–160, https://doi.org/10.1016/j.psyneuen.2016.04.008. Jul.
[71] A.C. Incollingo Rodriguez, L. Smith, R. Harris, B.C. Nephew, H.P. Santos Jr., C. Murgatroyd, Oxytocin modulates sensitivity to acculturation and discrimination stress in pregnancy, Psychoneuroendocrinology 141 (2022), 105769, https://doi.org/10.1016/j.psyneuen.2022.105769. Jul.
[72] S. Dewell, D. Slater, K. Benzies, S. McDonald, S. Tough, Relationship between psychosocial distress in pregnancy and two genes associated with human social interaction: a Pilot study, SAGE Open Nurs 4 (2018), 2377960818765272, https://doi.org/10.1177/2377960818765272. Jan-Dec.
[73] K.B. Michels, A.M. Binder, Considerations for design and analysis of DNA methylation studies, in: J. Tost (Ed.), DNA Methylation Protocols, Springer, New York, 2018, pp. 31–46.
[74] E. Unternaehrer, M. Bolten, I. Nast, et al., Maternal adversities during pregnancy and cord blood oxytocin receptor (OXTR) DNA methylation, Soc Cogn Affect Neurosci. 11 (9) (2016) 1460–1470, https://doi.org/10.1093/scan/nsw051. Sep.
[75] T.K. Robakis, S. Zhang, N.L. Rasgon, et al., Epigenetic signatures of attachment insecurity and childhood adversity provide evidence for role transition in the pathogenesis of perinatal depression, Transl. Psychiatry 10 (1) (2020) 48, https://doi.org/10.1038/s41398-020-0703-3. Feb 3.
[76] M. Galbally, J. Ryan, I.M. van, et al., Maternal depression, antidepressant use and placental oxytocin receptor DNA methylation: findings from the MPEWS study, Psychoneuroendocrinology 90 (2018) 1–8, https://doi.org/10.1016/j.psyneuen.2018.01.004. Apr.
[77] H. Cao, N. Zhou, E.M. Leerkes, J. Su, The etiology of maternal postpartum depressive symptoms: childhood emotional maltreatment, couple relationship satisfaction, and genes, J. Fam. Psychol. 35 (1) (2021) 44–56, https://doi.org/10.1037/fam0000722. Feb.
[78] J. Li, Y. Zhao, R. Li, L.S. Broster, C. Zhou, S. Yang, Association of oxytocin receptor gene (OXTR) rs53576 polymorphism with sociality: a meta-analysis, PLoS One 10 (6) (2015), e0131820, https://doi.org/10.1371/journal.pone.0131820.
[79] P. Gong, H. Fan, J. Liu, X. Yang, K. Zhang, X. Zhou, Revisiting the impact of OXTR rs53576 on empathy: a population-based study and a meta-analysis, Psychoneuroendocrinology 80 (2017) 131–136, https://doi.org/10.1016/j.psyneuen.2017.03.005. Jun.
[80] M.J. Bakermans-Kranenburg, I.M.H. van, The hidden efficacy of interventions: genexenvironment experiments from a differential susceptibility perspective,

Annu. Rev. Psychol. 66 (2015) 381–409, https://doi.org/10.1146/annurev-psych-010814-015407. Jan 3.
[81] P.D. Gluckman, M.A. Hanson, H.G. Spencer, Predictive adaptive responses and human evolution, Trends Ecol. Evol. 20 (10) (2005) 527–533, https://doi.org/10.1016/j.tree.2005.08.001. Oct.
[82] G. England-Mason, H.L. MacMillan, L. Atkinson, M. Steiner, A. Gonzalez, Emotion regulation moderates between maternal adverse childhood experiences (ACEs) and oxytocin response, Arch Womens Ment Health (2021), https://doi.org/10.1007/s00737-021-01194-5. Nov 9.
[83] M. Janecek, J. Dabrowska, Oxytocin facilitates adaptive fear and attenuates anxiety responses in animal models and human studies-potential interaction with the corticotropin-releasing factor (CRF) system in the bed nucleus of the stria terminalis (BNST), Cell Tissue Res. 375 (1) (2019) 143–172, https://doi.org/10.1007/s00441-018-2889-8. Jan.
[84] M. Galbally, E.F.C. van Rossum, S.J. Watson, E.R. de Kloet, A.J. Lewis, Trans-generational stress regulation: mother-infant cortisol and maternal mental health across the perinatal period, Psychoneuroendocrinology 109 (2019), 104374, https://doi.org/10.1016/j.psyneuen.2019.104374. Nov.
[85] M. Galbally, S.J. Watson, I.M. van, et al., The role of glucocorticoid and mineralocorticoid receptor DNA methylation in antenatal depression and infant stress regulation, Psychoneuroendocrinology 115 (2020), 104611, https://doi.org/10.1016/j.psyneuen.2020.104611. May.
[86] R.T. Amiel Castro, V. Glover, U. Ehlert, T.G. O'Connor, Antenatal psychological and socioeconomic predictors of breastfeeding in a large community sample, Early Hum. Dev. 110 (2017) 50–56, https://doi.org/10.1016/j.earlhumdev.2017.04.010. Jul.
[87] C.C. Dias, B. Figueiredo, Breastfeeding and depression: a systematic review of the literature, J. Affect. Disord. 171 (2015) 142–154, https://doi.org/10.1016/j.jad.2014.09.022. Jan 15.
[88] Y.X. Li, H. An, Z. Wen, Z.Y. Tao, D.Y. Cao, Can oxytocin inhibit stress-induced hyperalgesia? Neuropeptides 79 (2020), 101996 https://doi.org/10.1016/j.npep.2019.101996. Feb.
[89] S. Boll, A.C. Almeida de Minas, A. Raftogianni, S.C. Herpertz, V. Grinevich, Oxytocin and pain perception: from animal models to human research, Neuroscience 387 (2018) 149–161, https://doi.org/10.1016/j.neuroscience.2017.09.041. Sep. 1.
[90] J.A. Rash, A. Aguirre-Camacho, T.S. Campbell, Oxytocin and pain: a systematic review and synthesis of findings, Clin. J. Pain (30) (2014) 453–462.
[91] K. Buchanan, E. Newnham, D. Ireson, C. Davison, S. Bayes, Does midwifery-led care demonstrate care ethics: a template analysis, Nurs. Ethics (13) (2021).
[92] T.S. Eri, M. Berg, B. Dahl, H. Gottfreethsdottir, E. Sommerseth, C. Prinds, Models for midwifery care: a mapping review, Eur J Midwifery 4 (2020) 30, https://doi.org/10.18332/ejm/124110.
[93] S. Padmanabhan, A.F. Dominiczak, Genomics of hypertension: the road to precision medicine, Nat. Rev. Cardiol. 18 (4) (2021) 235–250, https://doi.org/10.1038/s41569-020-00466-4. Apr.
[94] A.M. Tsimberidou, E. Fountzilas, M. Nikanjam, R. Kurzrock, Review of precision cancer medicine: evolution of the treatment paradigm, Cancer Treat Rev. 86 (2020), 102019, https://doi.org/10.1016/j.ctrv.2020.102019. Jun.
[95] J.J. Scala, A.B. Ganz, M.P. Snyder, Precision medicine approaches to mental health care, Physiology 38 (2) (2023), https://doi.org/10.1152/physiol.00013.2022. Mar 1.
[96] S. Pauwels, L. Symons, E.L. Vanautgaerden, et al., The Influence of the Duration of Breastfeeding on the Infant's Metabolic Epigenome. Nutrients, 2019, pp. 1–14.
[97] V.V. Odintsova, F.A. Hagenbeek, M. Suderman, et al., DNA methylation signatures of breastfeeding in buccal cells collected in mid-childhood, Nutrients (2019) 1–26.
[98] Y. Mallisetty, N. Mukherjee, Y. Jiang, et al., Epigenome-wide association of infant feeding and changes in dna methylation from birth to 10 years, Nutrients (2021) 1–22.
[99] W.B. Sherwood, V. Bion, G.A. Lockett, et al., Duration of breastfeeding is associated with leptin (LEP) DNA methylation profiles and BMI in 10-year-old children, Clin Epigenetics: Clin. Epigenet. (2019) 1–10.
[100] F.P. Hartwig, C.L. De Mola, N.M. Davies, C.G. Victora, C.L. Relton, Breastfeeding effects on DNA methylation in the offspring: a systematic literature review, PLoS One 12doi (2017), https://doi.org/10.1371/journal.pone.0173070.
[101] O.Y. Naumova, V.V. Odintsova, I.A. Arincina, et al., A study of the association between breastfeeding and DNA methylation in peripheral blood cells of infants, Russ. J. Genet. (2019) 749–755.
[102] S. Cheshmeh, S.M. Nachvak, N. Rezvani, A. Saber, Effects of breastfeeding and formula feeding on the expression level of FTO, CPT1A and PPAR-alpha genes in Healthy infants, Diabetes Metab Syndr Obes 13 (2020) 2227–2237, https://doi.org/10.2147/DMSO.S252122.
[103] C.M. Heim, S. Entringer, C. Buss, Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health, Psychoneuroendocrinology: Elsevier (2019) 123–137.
[104] F.R. Walker, K. Pfingst, L. Carnevali, A. Sgoifo, E. Nalivaiko, In the search for integrative biomarker of resilience to psychological stress, Neurosci. Biobehav. Rev. 74 (Pt B) (2017) 310–320, https://doi.org/10.1016/j.neubiorev.2016.05.003. Mar.
[105] B.S. McEwen, Mood disorders and allostatic load, Biol Psychiatry 54 (3) (2003) 200–207, https://doi.org/10.1016/s0006-3223(03)00177-x. Aug 1.
[106] A. Flanagin, T. Frey, S.L. Christiansen, AMA Manual of style Committee. Updated guidance on the reporting of race and ethnicity in medical and science journals, JAMA 326 (7) (2021) 621–627, https://doi.org/10.1001/jama.2021.13304.
[107] N.T. Buchanan, M. Perez, M.J. Prinstein, I.B. Thurston, Upending racism in psychological science: Strategies to change how science is conducted, reported, reviewed, and disseminated, Am. Psychol. 76 (7) (2021) 1097–1112, https://doi.org/10.1037/amp0000905. Oct.
[108] P.R. Butovskaya, O.E. Lazebny, E.M. Sukhodolskaya, et al., Polymorphisms of two loci at the oxytocin receptor gene in populations of Africa, Asia and South Europe, BMC Genet. 17 (2016) 17, https://doi.org/10.1186/s12863-015-0323-8. Jan 6.