Current Psychiatry Reports (2018) 20: 102
https://doi.org/10.1007/s11920-018-0961-4

SEX AND GENDER ISSUES IN BEHAVIORAL HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

Sex Differences in Vulnerability to Prenatal Stress: a Review of the Recent Literature

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Published online: 18 September 2018

Abstract

Purpose of Review To evaluate the degree to which recent studies provide evidence that the effects of prenatal maternal stress (PNMS) on child health outcomes vary depending on the child's biological sex. In this review, we used a broad definition of stress, including negative life events, psychological stress, and established stress biomarkers. We identified 50 peer-reviewed articles (published January 2015–December 2017) meeting the inclusion criteria.

Recent Findings Most articles ($k = 35$) found evidence of either sex-specific associations (significant in one sex but not the other) or significant PNMS^{x}stress interactions for at least one child health outcome. Evidence for sex-dependent effects was strongest in the group of studies evaluating child neural/nervous system development and temperament as outcomes.

Summary There is sufficient evidence of sex-dependent associations to recommend that researchers always consider the potential role of child sex in PNMS programming studies and report descriptive statistics for study outcomes stratified by child biological sex.

Keywords Prenatal maternal stress · Prenatal programming · Pregnancy · Sex as a biological variable · Child health · Effect modification

Introduction

There is compelling evidence that children exposed to high levels of prenatal stress are at risk for a host of adverse health outcomes [1–7]. Prenatal maternal stress (PNMS) increases fetal exposure to stress biomarkers (e.g., cortisol and pro-inflammatory cytokines) and may alter the development of critical biological systems (e.g., the endocrine, immune, and nervous systems) [8–10]. This confers lasting susceptibility to health complications in the child [2, 4–6] and potentially transgenerational risks through epigenetic programming [8, 9, 11]. There is also accumulating evidence that the child's biological sex may modify the effect of PNMS on child health [12–15]. Consequently, many scholars have underscored the need to evaluate for sex-dependent effects in PNMS programming models [12, 13, 15–18].

The potential sex-dependent nature of PNMS programming is intuitive given well-established sex differences in human embryonic and fetal development [19, 20]. The placenta is sexually dimorphic both in terms of its biological makeup [15, 20] and its adaptations within the intrauterine environment [12, 15, 16, 20, 21]. Female and male fetuses generally employ different evolutionary strategies to optimize fitness. Males invest heavily in growth but are less adaptable to environmental challenges in utero. In contrast, female fetuses are more responsive to environmental stress signals and are better able to adapt to prenatal insults (e.g., deficient nutrient supply) [13, 15, 16, 20, 21]. The female fetus is also better protected

This article is part of the Topical Collection on *Sex and Gender Issues in Behavioral Health*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11920-018-0961-4) contains supplementary material, which is available to authorized users.

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from inflammatory processes that could compromise viability [13, 16]. Thus, females are better positioned to survive suboptimal intrauterine conditions, whereas males are more susceptible to severe consequences of intrauterine adversity (e.g., mortality or pervasive disability) [12]. However, the female viability advantage appears to come with increased vulnerability to less severe but lasting health complications (e.g., anxiety and depression) [12–14]. PNMS programming of HPA-axis sensitivity and internalizing behaviors in females may also promote adaptive caregiving behaviors that increase survival in the next generation [17].

In sum, PNMS is hypothesized to alter embryonic and placental functioning, contributing to lifespan health complications. There is accumulating evidence for sex differences in PNMS programming models and strong biological plausibility given the sexually dimorphic nature of prenatal development.

The purpose of this paper is to review the recent literature evaluating sex-dependent effects of PNMS on child health outcomes. Clarifying the nature of sex-dependent PNMS programming may lead to a stronger understanding of lifelong disease processes and facilitate tailored intervention approaches. We conceptualized "stress" broadly, including psychological distress (e.g., perceived stress and psychopathology symptoms), challenging life events (e.g., daily hassles and natural disasters), and established stress biomarkers (e.g., maternal cortisol). For clarity, we distinguish between two types of *sex-dependent* associations. S*ex-specific* effects indicate that the PNMS➔outcome association is significant for one sex but not the other. Importantly, a sex-specific association does *not* provide evidence that the PNMS➔outcome association was significantly stronger in one sex than the other. *Sex interactions*, in contrast, indicate that the magnitude of the PNMS➔outcome association differs significantly for female and male offspring.

Method

We searched PubMed on January 18, 2018, for articles evaluating associations between PNMS and child health outcomes. We limited the results to human-subject studies published in English between January 2015 and December 2017 (see online supplement for search criteria). The primary search returned 2805 abstracts (Fig. 1), which were screened by the authors and included if they:

1. Measured prenatal maternal stress as an exposure variable
2. Measured some form of offspring health or development as an outcome, with no restrictions on offspring age at the time of outcome ascertainment
3. Described an empirical study published in a refereed journal
4. Reported evaluating whether PNMS programming effects were sex-dependent

We found additional articles by conducting a secondary Google Scholar search (using the same search criteria) and by reviewing reference lists of relevant papers.

Results

We identified 50 peer-reviewed articles meeting the inclusion criteria (Table 1). The majority of included articles reported at least one sex-dependent association ($k = 35$; 70%), either PNMS^{x}sex interactions ($k = 17$; 34%) or sex-specific effects ($k = 18$; 36%). Most studies had modest sample sizes ($Mdn =$ 205.5, first quartile = 107.2, third quartile = 465.0), and it is likely that most were not optimally powered to detect sex differences [71, 72]. Studies reporting sex-dependent associations (either sex-specific associations or interactions) had a similar median sample size ($Mdn = 216$) compared to those that did not ($Mdn =$ 194): $W = 247$, $p = .75$. Similarly, studies finding significant sex interactions had a similar median sample size ($Mdn =$ 212) compared to those that did not ($Mdn =$ 199): $W = 304$, $p = .64$.

For ease of presentation, we grouped the results into three major categories based on types of child health outcomes: physical health and development, cognitive development, and emotional/behavioral health (Table 2). Eight studies reported evaluating for sex-dependent associations with outcomes from multiple child health categories.

Physical Health and Development Outcomes

Thirty papers evaluated sex-dependent associations related to the child's physical health or development. We further divided these papers into six subcategories.

Respiratory Health Wright and colleagues published three papers focused on the effects of prenatal negative life events (PNLEs) on respiratory outcomes, with two reporting sex-dependent associations. Lee et al. found negative associations between PNLEs and several indicators of lung function at age 7 ($N = 199$), with no evidence of sex-dependent associations [28]. A second paper by this group ($N = 765$) showed a sex-dependent association whereby PNLEs were associated with increased odds of asthma at age 4 in boys but not girls. However, among girls, there was evidence of a combined effect of prenatal and postnatal stress on the odds of asthma [58•]. In the third study ($N = 417$), there was a sex-specific association whereby PNLEs were positively associated with risk for lifetime wheeze at age 4 among boys only [59].

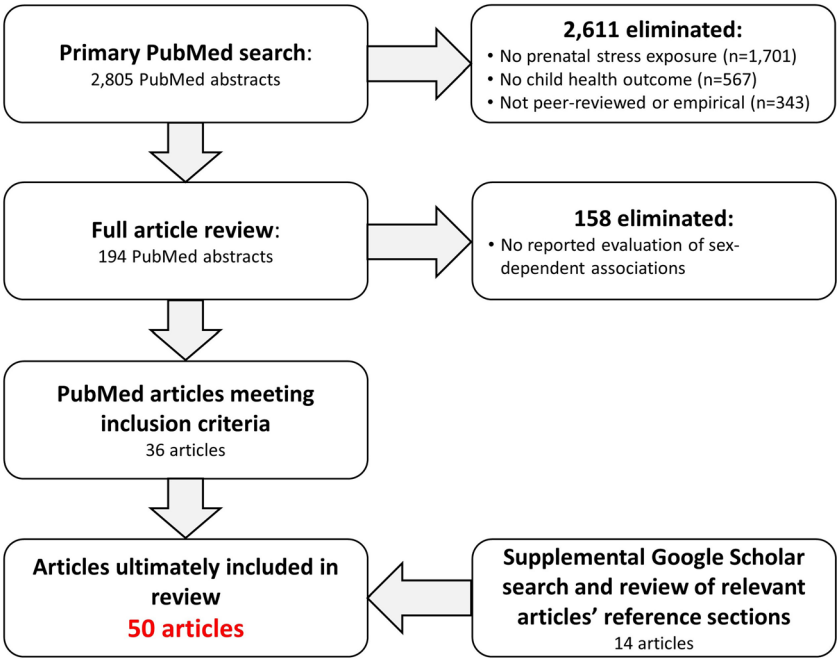

Fig. 1 Literature review search strategy results

Fetal/Neonatal Health Four studies evaluated fetal/neonatal health outcomes with two reporting sex-dependent associations. Edwards et al. ($N = 196$) evaluated the association between prenatal maternal depression and a global measure of neonatal health problems (e.g., prematurity, low Apgar scores, low birth weight), with no evidence of sex-dependent associations [73]. Within the context of a randomized controlled trial ($N = 1041$), Frith et al. found that maternal prenatal salivary cortisol concentration was negatively associated with infant birth weight and head circumference *only* among male children whose mothers were randomized to the usual care condition [56]. Kaitz et al. ($N = 212$) reported significant interactions between maternal third trimester anxiety and child sex in predicting both third trimester fetal weight and birth weight. In both cases, boys weighed more than girls when exposed to prenatal anxiety, but there were no sex differences in its absence [45•]. Finally, Giesbrecht et al. ($N = 291$) reported that fetal sex appeared to have an effect on maternal prenatal stress physiology (salivary alpha-amylase and cortisol), which in turn was associated with child birth weight. However, there was no evidence that the strength of the association between maternal stress physiology and child birth weight differed by child sex [26].

Body Composition Four studies evaluated child body composition with none finding sex-dependent associations. (Note, studies evaluating fetal weight and birth weight were included in the Fetal/Neonatal Health section.) In the Iowa Flood Study ($N = 106$), there was no evidence of sex-dependent associations between PNMS related to a flooding disaster and early childhood BMI and adiposity [32]. Similarly, data from the Quebec Ice Storm study ($N = 111$) showed no evidence of sex-dependent associations between disaster-related PNMS and child adiposity or BMI (ages 5–15) [31]. Data from Project Viva ($N = 1116$) provided no evidence of sex-dependent associations between maternal second trimester biomarkers of inflammation and child adiposity outcomes [24]. Finally, Entringer et al. ($N = 67$) found a positive association between maternal prenatal cortisol production and the rate of increase in infant percent body fat from 1 to 6 months of age, with no evidence of that the association was sex-dependent [35].

Motor Development Four studies examined child motor development with two reporting sex-dependent associations. The Queensland Flood Study team reported associations between disaster-related PNMS and infant motor outcomes in two papers. In the first ($N = 130$), there was no evidence of sex-dependent associations between disaster-related PNMS and infant motor development [30]. In the second ($N = 145$), there was a near-significant interaction between maternal negative cognitive appraisal of flood-related stress and child sex predicting 16-month gross motor skills. Negative cognitive appraisal of the disaster was associated with poorer motor development among girls but not boys [66]. Bandoli et al. examined effects of prenatal alcohol exposure and maternal depression on child psychomotor development at 6 and 12 months of age ($N = 344$). In the group of infants with prenatal alcohol exposure, there was a significant interaction of maternal prenatal depressive symptoms and child sex in predicting motor development. Among alcohol-exposed girls, but not boys, maternal prenatal depressive symptoms were positively associated with 6-month motor deficits [41•].

Table 1 Characteristics of articles included in the review

Article	*N*	Prenatal maternal stress exposure variable	Timing of exposure measurement	Child health outcome categories
No sex-dependent effect[a] ($k = 15$; 30%)				
[22•]	9166	Life events; psychological: perceived impact of events	18-week gestations	Emotional/behavioral: depression/anxiety symptoms
[23][b]	6969 and 425	Psychological: anxiety and depression	18- and 32-week gestation	Cognitive development; emotional/behavioral: ADHD/conduct symptoms
[24]	1116	Biological: C-reactive protein plasma level	Second trimester	Physical: body composition
[25]	481	Psychological: perceived stress and depression	28-week gestation	Physical: neural/nervous system development
[26]	291	Biological: maternal cortisol and salivary alpha-amylase; psychological: depression and anxiety	22-week and 32-week gestation	Physical: fetal/neonatal health
[27]	288	Psychological: anxiety and depression	28–32-week gestation	Physical: motor development; cognitive development; emotional/behavioral: ADHD/conduct symptoms and broad psychopathology measures
[28]	199	Life events	$M = 28.4$-week gestation	Physical: respiratory health
[29]	194	Biological: salivary cortisol; psychological: depression	14- and 32-week gestation	Physical: neural/nervous system development
[30]	130	Natural disaster; psychological: perceived impact of events and related symptoms	Any time during pregnancy	Physical: motor development
[31]	111	Natural disaster; psychological: perceived impact of events and related symptoms	Various times in pregnancy	Physical: body composition
[32]	106	Natural disaster; psychological: perceived impact of events and related symptoms	Various times in pregnancy	Physical: body composition
[33]	91	Biological: plasma cortisol	19- and 31-week gestation	Physical: neural/nervous system development; cognitive development
[34]	88	Psychological: depression; biological: cortisol reactivity	Second or third trimester	Physical: neural/nervous system development
[35]	67	Biological: cumulative cortisol production	Repeated throughout pregnancy	Physical: body composition
[36]	54	Natural disaster; psychological: perceived impact of events	Any time during pregnancy	Emotional/behavioral: eating disorder symptoms
Significant sex interaction[c] ($k = 17$; 34%)				
[37•]	7959	Psychological: depression	18- and 32-week gestation	Emotional/behavioral: depression/anxiety symptoms
[38]	1258	Biological: inflammatory cytokines	Late second or early third trimester	Emotional/behavioral: depression/anxiety symptoms
[39]	1195	Psychological: anxiety and depression	17- and 30-week gestation	Emotional/behavioral: ADHD/conduct symptoms
[40]	885	Psychological: depression	Third trimester	Emotional/behavioral: broad psychopathology measures
[41•]	344	Psychological: depression	32-week gestation	Physical: motor development; cognitive development
[42•]	301	Life events; psychological: anxiety, negative affect	Second trimester	Emotional/behavioral: schizophrenia spectrum disorders
[43]	236	Biological: cortisol; psychological: distress	14 weeks and 32 weeks	Physical: neural/nervous system development
[44•]	216	Biological: cortisol	Measured at 32 weeks	Emotional: temperament
[45•]	212	Psychological: anxiety	Third trimester	Physical: fetal/neonatal health
[46]	125	Psychological: negative mood; biological: cortisol, diastolic blood pressure, immune markers	Second and third trimester	Physical: neural/nervous system development
[47]	121	Natural disaster; psychological: perceived impact of events and related symptoms	General pregnancy (timing measured)	Emotional/behavioral: temperament
[48]	115	Natural disaster; psychological: perceived impact of events and related symptoms	General pregnancy (timing measured)	Cognitive development

Table 1 (continued)

Article	*N*	Prenatal maternal stress exposure variable	Timing of exposure measurement	Child health outcome categories
[49]	94	Natural disaster; psychological: perceived impact of events and related symptoms	General pregnancy	Physical: neural/nervous system development
[50]	88	Biological: cortisol and salivary alpha amylase; psychological: depression	27-week gestation	Emotional/behavioral: temperament
[51]	57	Psychological: depression; biological: cortisol	Second or third trimester	Physical: neural/nervous system development
[52]	52	Psychological: depression	Measured in each trimester	Physical: neural/nervous system development
[53]	45	Psychological: anxiety	Measuring in each trimester	Physical: neural/nervous system development
Sex-specific effect[d] ($k = 18$; 36%)				
[54]	1765	Life events	Cumulative: prenatal report	Emotional/behavioral: ADHD/conduct symptoms
[55]	1214	Life events	18- and 34-week gestation	Emotional/behavioral: depression/ anxiety symptoms
[56]	1041	Morning cortisol concentration	28–32-week gestation	Physical: fetal/neonatal health
[57•]	813	Psychological: anxiety, depression	First and second trimester	Emotional/behavioral: broad psychopathology measures
[58•]	765	Life events	Cumulative: prenatal report	Physical: respiratory health
[59]	417	Life events	Second or third trimester	Physical: respiratory health
[60]	262	Biological: cortisol	Third trimester	Physical: adult cardiovascular health
[61•]	258	Psychological: depression	Second trimester	Physical: neural/nervous system development; emotional/behavioral: broad psychopathology measures
[62]	236	Life events; psychological: anxiety, depression	Cumulative: prenatal report	Cognitive development
[63]	235	Psychological: depression	Measured at 26 weeks	Physical: neural/nervous system development
[73]	196	Psychological: depression	Cumulative: prenatal report	Emotional/behavioral: broad psychopathology measures; physical: fetal/neonatal
[64]	158	Psychological: perceived stress; life events	Any time during pregnancy	Physical: neural/nervous system development
[65]	153	Psychological: depression	Any time during pregnancy or within 3 months of conception	Physical: neural/nervous system development
[66]	145	Natural disaster; psychological: perceived impact of events and related symptoms	Pregnancy	Cognitive development; physical: motor development
[67]	130	Natural disaster; psychological: perceived impact of events and related symptoms	General pregnancy (timing measured)	Cognitive development
[68]	93	Psychological: anxiety and depression; biological: cortisol	17 and 28 weeks of gestation	Physical: neural/nervous system development
[69]	90	Psychological: anxiety	20.5-week gestation	Emotional/behavioral: temperament
[70•]	49	Biological: cortisol; psychological: anxiety, depression	Five times throughout pregnancy	Physical: neural/nervous system development; emotional/behavioral: broad psychopathology measures

[a] Articles evaluating sex-dependent associations between prenatal stress and child health outcomes but found no evidence of sex dependence

[b] This article included two studies and sample sizes for both are listed

[c] Articles reporting significant stress[x] sex interactions in predicting child health outcomes

[d] Articles reporting significant sex-specific associations between the exposure and outcome (a significant association in one sex but not the other)

Table 2 Evidence of sexual dimorphism by outcome category

	k[a]	Studies with sex-specific associations[b]	Studies with sex interactions[c]
Physical health and development	32		
Respiratory health	3	$k = 2$: [58•, 59]	None
Fetal/neonatal health	4	$k = 1$: [56]	$k = 1$: [45•]
Body composition	4	None	None
Motor development	4	$k = 1$: [66]	$k = 1$: [41•]
Adult cardiovascular health	1	$k = 1$: [60]	None
Neural/nervous system development	16	$k = 6$: [61•, 63, 64, 65, 68, 70•]	$k = 6$: [43, 46, 49, 51–53]
Cognitive development	8	$k = 2$: [62, 67]	$k = 2$: [41•, 48]
Emotional/behavioral health	19[d]		
Temperament	4	$k = 1$: [69]	$k = 3$: Braithwaite, [47, 50, 57•]
Broad psychopathology measures	6	$k = 4$: [57•, 61•, 70•, 73]	$k = 1$: [40]
Depression/anxiety symptoms	5	$k = 1$: [55]	$k = 2$: [37•, 38]
ADHD/conduct symptoms	4	$k = 1$: [54]	$k = 1$: [39]
Eating disorder symptoms	1	None	None
Schizophrenia spectrum disorders	1	None	$k = 1$: [42•]

[a] Number of studies within each child health outcome category with some studies measuring outcome variable from multiple categories

[b] Indicates that the exposure➔outcome association was significant in one sex but not the other

[c] Indicates that the effect among boys and girls differed significantly

[d] The number of studies summed across the subcategories exceeds this total number (representing the total number of unique studies measuring emotional/behavioral health outcomes) because some studies measured multiple emotional/behavioral health outcomes across subcategories and are included in multiple rows

Finally, in a prospective birth cohort study ($N = 288$), there was no evidence of sex-dependent associations between maternal psychopathology symptoms and child motor skills at age 4 [27].

Adult Cardiovascular Health One study ($N = 262$) examined prenatal cortisol exposure and adult offspring coronary heart disease risk (mean age = 42) by evaluating data on risk factors such as diabetes and blood pressure. There was evidence of a sex-specific effect with increased cardiovascular risk associated with maternal cortisol only in female adult offspring [60].

Neural/Nervous System Development Sixteen papers evaluated indicators of child neural and/or nervous system development with 12 reporting sex-dependent associations. Five evaluated effects of PNMS on neural structure and function, four providing evidence of sexually dimorphic programming effects in girls. Wen et al. ($N = 235$) reported a sex-specific association whereby prenatal depression was positively associated with greater right amygdala volume in 4.5-year-old girls, but not boys [63]. Data from the same study team ($N = 258$) showed that, among girls only, increases in maternal depressive symptoms from 26-week gestation to 3 months postpartum were associated with greater infant right frontal lobe activity and greater right frontal asymmetry at age 6 months and greater lower right frontal functional connectivity at age 18 months [61•]. Kim et al. ($N = 49$) found that, among girls only, prenatal exposure to maternal cortisol was associated with altered neural activity and connectivity at ages 6–9, which in turn mediated the association between prenatal cortisol and internalizing symptoms [70•]. Lebel et al. ($N = 52$) reported a significant interaction between child sex and second trimester maternal depressive symptoms in predicting cortical thickness in the right-middle temporal region. Maternal depression was negatively associated with cortical thickness with the association significantly stronger in girls than boys [52]. Finally, Davis et al. ($N = 91$) found significant associations between third trimester maternal cortisol concentrations and brain development, but no evidence of sex dependence [33].

Five studies evaluated associations between PNMS and child neuroendocrine functioning as indicated by cortisol concentrations, four indicating sex-dependent associations. Data from the Iowa Flood Study ($N = 94$) showed evidence of an interaction: There was a positive association between maternal flood-related subjective stress and child salivary cortisol reactivity (age 2.5 years) among girls, whereas the association was in the opposite direction among boys [49]. Giesbrecht et al.

($N = 236$) found multiple sex interactions. Less prominent cortisol awakening responses and flatter daytime cortisol slopes in pregnant mothers were associated with blunted cortisol response in infant girls, but the opposite was true in boys. Further, cortisol reactivity in girls differed depending on the combined levels of prenatal maternal distress and cortisol levels. Girls, but not boys, exposed to both low levels of prenatal maternal cortisol *and* high levels of maternal distress showed elevated stress reactivity at age 3 [43]. Stroud et al. ($N = 153$) reported a sex-specific effect whereby maternal prenatal major depressive disorder (MDD) was associated with increased infant salivary cortisol reactivity among girls but not boys. Further, among girls only, the positive association between prenatal maternal depressive symptoms on infant baseline cortisol levels was present at low but not high levels of methylation of the placental glucocorticoid gene *HSD11B2*. In contrast, prenatal MDD was associated with increased infant cortisol levels among boys only in combination with very low or high levels of expression of the placental serotonin gene *SLC6A4* [65]. Gholipoor et al. ($N = 158$) found a sex-specific effect among young children (ages 0–2): Higher maternal prenatal perceived stress was positively associated with circulating levels of blood cortisol among girls but not boys [64]. Finally, Braithwaite ($N = 88$) found no evidence of associations—sex-dependent or otherwise—between maternal PNMS (depressive symptoms and salivary cortisol reactivity) and infant salivary cortisol reactivity in response to a standard pediatric inoculation [34].

Four papers described epigenetic studies evaluating associations between PNMS and the expression of genes involved in stress and emotion regulation, with three reporting sex-dependent associations. Braithwaite et al. ($N = 57$) reported an interaction such that maternal prenatal depressive symptoms were positively associated with buccal swab levels of DNA methylation of the *NR3C1* glucocorticoid receptor gene in infant boys but not girls. But there was no evidence of sexually dimorphic effects of maternal prenatal cortisol in this study [51]. Similarly, Vangeel et al. ($N = 45$) found an interaction such that prenatal anxiety was positively associated with cord blood DNA methylation in the GABA-B receptor subunit 1 gene (*GABBR1*) in infant boys but not girls [53]. Mina et al. found sex-specific associations suggesting that infant girls might be particularly susceptible to the effects of prenatal maternal distress on placental mRNA levels of genes regulating fetal glucocorticoid exposure and placental growth [68]. Finally, data from the Barwon Infant Study ($N = 481$) showed no evidence of sex dependence in associations between PNMS and cord blood *NR3C1* glucocorticoid receptor gene methylation [25].

Two papers describe studies evaluating other indicators of nervous system development. Doyle et al. ($N = 125$) reported several sex interactions in associations between both psychological (negative mood) and biological (salivary cortisol, blood pressure) markers of PNMS and indicators of fetal central and autonomic nervous system development (heart rate and movement). Findings generally showed that PNMS was associated with variable deviations from normal development in female fetuses, whereas PNMS was associated with consistently accelerated development in males [46]. In contrast, data from the Alberta Pregnancy Outcomes & Nutrition study ($N = 194$) found no evidence of sex-dependent associations when evaluating effects of both prenatal maternal cortisol and depressive symptoms on an indicator of offspring parasympathetic nervous system functioning (cardiac vagal control) at age 6 months [29].

Cognitive Development

Eight papers evaluated child cognitive development, with four reporting sex-dependent associations. Three papers reported data from the Queensland Flood Study. Simcock et al. ($N = 115$) found a sex interaction in the association between disaster-related PNMS and child problem solving at age 6 months, with girls having poorer problem solving than boys at high levels of prenatal stress [48]. In contrast, Moss et al. ($N = 145$) found no evidence of sex dependence in the association between PNMS and adolescent cognitive development [66]. In the final paper from this group ($N = 130$), there was a sex-specific effect whereby PNMS was associated with poorer theory of mind in 30-month-old girls but not boys [67].

Plamondon et al. ($N = 236$) showed that, among both sexes, PNLEs were associated with poorer working memory; however, there was a sex-specific effect whereby adaptive parenting behaviors buffered against the adverse effect of PNLEs among boys, but not girls [62]. Bandoli et al. also reported a sex interaction ($N = 344$): Prenatal depression, in conjunction with prenatal alcohol exposure, was associated with developmental deficits in 6-month-old girls, but not boys [41•]. In contrast, several studies provided no evidence of sex-dependent effects of PNMS on child cognitive development. Investigators from the Rhea Study ($N = 288$) found no evidence for sex dependence in the association between PNMS and child cognitive development at age 4 [27]. Davis et al. ($N = 91$) found no evidence of a sex-dependent association between maternal prenatal plasma cortisol concentrations and child (ages 6–9) cognitive functioning [33]. Finally, data from two independent cohorts ($N = 6969$ and $N = 425$) provided no evidence of sex dependence in an association between prenatal maternal anxiety and offspring working memory [23].

Emotional/Behavioral Health

Nineteen papers evaluated child emotional/behavioral health outcomes. For ease of interpretation, we grouped them into five subcategories.

Temperament Four papers examined child temperament, all finding evidence of sex-dependent effects. Braithwaite et al.

($N = 216$) found a sex interaction such that 5-week-old girls exposed to maternal cortisol exhibited elevated negative emotionality, whereas cortisol-exposed boys exhibited attenuated negative emotionality [44•]. They then replicated this interaction effect in an independent sample ($N = 88$) of 2-month-old infants [50]. However, findings from the Queensland Flood Study ($N = 121$) showed an interaction with a contrasting pattern: disaster-related PNMS was associated with increased irritability in boys and was unrelated to irritability in girls [47]. Finally, data from the Prenatal Early Life Stress Project ($N = 90$) reported no sex dependence in the association between prenatal anxiety and infant temperament at 9–14 months; however, there was a sex-specific indirect effect of maternal prenatal mindfulness on infant self-regulation problems via prenatal maternal anxiety for boys only [69].

Broad Psychopathology Measures Six studies evaluated broad measures of psychopathology—including symptoms from multiple psychiatric disorders—with five showing evidence of sex-dependent associations. Investigators from the Rhea Study ($N = 288$) found no evidence of sex dependence in the association between prenatal psychopathology symptoms and 4-year-old behavioral outcomes [27]. Data from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort ($N = 258$) showed that maternal prenatal depressive symptoms were positively associated with both internalizing and externalizing symptoms at age 2 among girls, but only internalizing symptoms in boys [61•]. In a study of young African-American mothers and their offspring ($N = 196$), prenatal depressive symptoms were indirectly associated with increased child social/emotional problems at age 2 through postnatal maternal depressive symptoms and maternal parenting sensitivity, but this effect was significant only among boys [73]. Similarly, a community-based cohort study ($N = 885$) found a significant interaction between prenatal maternal depression and child sex in predicting a broad measure of social-emotional well-being at age 7: Prenatal maternal depression was associated with much higher levels of emotional-behavioral problems among boys and was not significant for girls [40]. Pickles et al. ($N = 813$) found that the adverse effects of prenatal pregnancy-specific anxiety on child internalizing and externalizing symptoms at age 3.5 were ameliorated by maternal-infant stroking. Interestingly, the buffering effect of infant stroking was only significant for girls [57•]. Kim et al. ($N = 49$) reported a positive association between maternal prenatal plasma cortisol concentrations and internalizing problems in girls only, with the effect mediated by changes in brain networks [70•].

Depression/Anxiety Symptoms Five studies examined child depression and/or anxiety outcomes, with three finding sex-dependent associations. Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC; $N = 7959$), Quarini et al. reported a significant sex interaction: Prenatal depression was associated with elevated odds of depression among 18-year-old girls, whereas there was a tendency for reduced odds for exposed boys. Prenatal depression was associated with increased odds of depression at age 12 regardless of child sex [37•]. In a second analysis from ALSPAC ($N = 9166$), maternal PNLEs were positively associated with offspring depressive symptoms and diagnosis at age 17–18, with no evidence of sex dependence [22•]. Using data from the Western Australian Pregnancy Cohort ($N = 1214$), Herbison et al. found that prenatal stress was positively associated with depression/anxiety symptoms at age 20 in male but not female offspring after adjusting for postnatal childhood stress trajectories [55]. In the Preschool ADHD study, Bendiksen et al. [39] found no evidence of sex dependence in the association between maternal prenatal anxiety and depression symptoms and early childhood anxiety symptoms [39]. Finally, in a case-control study ($N = 1258$), Gilman et al. evaluated the association between maternal inflammatory cytokines and odds of major depressive disorder (MDD) in adult offspring (mean age 39.7). There was a significant interaction whereby a higher ratio of maternal prenatal pro- to anti-inflammatory cytokines was associated with reduced odds of MDD in women and increased odds in men [38].

Attention Deficit/Hyperactivity and Conduct Symptoms Four studies examined symptoms of attention deficit/hyperactivity disorder (ADHD) and/or conduct disorder, with two finding sex-dependent associations. Bendiksen et al. ($N = 1195$) found evidence of sex interactions: Maternal prenatal psychopathology symptoms were associated with increased odds of conduct symptoms in boys, but not girls [39]. Zhu et al. ($N = 1765$) found a sex-specific association: Severe PNLEs were associated with increased odds of clinical ADHD symptoms in preschool boys but not girls [54]. In the ALSPAC data ($N = 6969$), there was a significant interaction of maternal anxiety and a *COMT* genetic variation in predicting child ADHD symptoms at age 4, but no evidence of sex dependence [23]. Finally, in the Rhea Study ($N = 288$), maternal psychopathology symptoms were associated with child ADHD symptoms, but there was no evidence of sex dependence [27].

Eating Pathology St-Hilaire et al. ($N = 54$) found no evidence of sex dependence in the association between disaster-related PNMS in the third trimester and eating disorder pathology. However, the study was under-powered for this purpose [36].

Schizophrenia Spectrum Disorders Fineberg et al. ($N = 301$) evaluated odds of offspring schizophrenia spectrum disorders (SSD) and reported a significant interaction of prenatal daily life stressors and child sex. Among boys, PNMS was associated with significantly increased odds of SSD, whereas there was a trend for reduced odds among girls [42•].

Discussion

The fact that we identified 50 published articles evaluating the potential sex-dependent nature of PNMS effects on child health outcomes within a 3-year span is evidenced that many researchers are heeding recommendations [12, 15–17, 20] to consider the role of the child's biological sex in PNMS programming. Our findings reinforce this recommendation. The majority of articles reviewed found a sex-dependent association with at least one child outcome, and a substantial minority reported a significant PNMS^{x}sex interaction. These results, in combination with strong biological evidence for sexually dimorphic prenatal development [12, 13, 15, 16, 19–21] and findings from prior reviews [12–14, 16, 17, 21], send a clear message that a child's biological sex should always be considered in mixed-sex PNMS programming studies.

This is not to say that PNMS effects on child outcomes are invariably sex-dependent. In fact, we identified three large—and presumably well-powered—studies (Ns > 1000) that found evidence for PNMS programming but no sex-dependent associations [22•, 23, 24]. It is not yet clear why a child's biological sex modifies PNMS programming in certain contexts and not others. Until we have a stronger understanding of these inconsistencies, we recommend that researchers conduct and report formal evaluations of sex dependencies and that journal reviewers and editors request these analyses if they are absent. Although many small-sample studies will not be optimally powered to detect sex-dependent effects, reporting descriptive statistics for outcome variables stratified by child sex could enable well-powered meta-analytic evaluations.

The strongest evidence for sex-dependent programming effects in this review came from studies evaluating offspring neural/nervous system development and temperament. Twelve of the 16 articles evaluating neural/nervous system development showed sex-dependent associations. Six reported significant PNMS*sex interactions. The preponderance of evidence suggests that girls may be particularly vulnerable to PNMS programming, altering neural structure, function, and neuroendocrine sensitivity in a manner that confers risk for anxiety and affective pathology [61•, 63, 70•]. One study found evidence that these neural sequelae may mediate PNMS effects on internalizing symptoms [70•].

All four studies evaluating programming effects on child temperament reported sex-dependent associations. Two reported significant sex interactions suggesting that PNMS is associated with elevated negative emotionality and reactivity in girls and decreased emotionality and reactivity in boys [44•, 50]. These findings are generally in keeping with preexisting scholarship [12, 14, 17] and theories positing a lasting PNMS-driven vulnerability to mood and anxiety problems in females and fear inhibition in males [12, 17]. A third study, however, found a significant interaction indicating increased infant irritability only in boys exposed to PNMS [47]. Thus, there are likely other factors (e.g., timing of exposure and outcome ascertainment) that may alter the sex-dependent nature of the association between PNMS and offspring temperament.

This review also found some indication of sexually dimorphic effects of PNMS on other child health outcomes. Among female offspring, there was greater evidence for positive associations between PNMS and early childhood difficulties with cognitive [48, 67] and motor development [41•, 66], and adulthood cardiovascular disease risk [60]. In contrast, we uncovered greater evidence for PNMS sensitivity in male offspring for early childhood wheezing/asthma [58•, 59], externalizing pathology [39, 54], and schizophrenia spectrum disorders [42•]. It is noteworthy that males have a greater risk in the general population for all of the adverse health outcomes showing male-biased PNMS programming effects in this review (early childhood asthma/wheezing [58•, 59, 74], externalizing pathology [39, 54, 75], and schizophrenia spectrum disorders [42•, 76]). It may be that PNMS contributes to, or exacerbates, vulnerabilities for these sexually dimorphic health conditions [77]. Alternatively, it is plausible that there was simply more power to detect associations between PNMS and these health conditions in males because the conditions are more common among males in the population.

Findings from a couple of studies were notably consistent with the evolutionary perspective that male fetuses continue to prioritize growth and physical development in the presence of intrauterine adversity, whereas female fetuses modulate growth to improve viability [12, 16, 17]. Kaitz et al. found that male fetuses and neonates were larger than females only when exposed to PNMS [45•]. Likewise, Doyle et al. found that PNMS was associated with variable deviations from typical development in female fetuses and consistently accelerated development in male fetuses [46]. These results reinforce the potential value of evolutionary biology frameworks [12, 16, 17, 19] for understanding sex-dependent PNMS programming.

Limitations and Future Directions

This review included only studies that reported evaluating sex dependence in PNMS programming, likely providing a biased sample of the broader literature. Studies finding sex-dependent associations were probably more likely to report these analyses and be included in this review. Additionally, many studies included multiple PNMS exposure variables and child health outcomes, increasing the risk for type I errors. Thus, our results may overestimate the likelihood of sex-dependent associations. On the other hand, researchers typically power studies to detect main effects and not effect modification, meaning that if sex-dependent PNMS associations exist in the population, many studies will fail to detect them.

A critical future task, if we are to fully understand the nature of PNMS programming, is to explicate the processes that moderate and mediate effects on child health outcomes. This is challenging given the complexity of both the intrauterine and maternal environments and their interactions [16]. Detecting effect modification and mediation requires large sample sizes [71, 72]. Implementing studies that satisfy power projections while also optimizing the research design (e.g., repeated collection of biomarkers) would be challenging and costly. To further complicate matters, a number of studies have shown that PNMS^{x}sex interactions are dependent on other factors, creating higher-order interactions. The most well-established of these factors is timing of exposure [77, 78], which was highlighted by many studies in this review [29, 36, 39, 43, 46, 49, 54, 66, 70•]. Finally, including child sex as a moderator may be insufficient: Evaluating PNMS programming may require entirely different models with different functional forms for girls and boys. Combining datasets using advancing data harmonization methods [79] may allow for increased statistical power and improved understanding of how child sex influences the hypothesized causal pathway from PNMS to offspring health outcomes.

Conclusions

This review found substantial—albeit somewhat inconsistent—evidence of sex-dependent prenatal maternal stress (PNMS) associations with child health outcomes in articles published between January 2015 and December 2017. There was strong evidence for sexual dimorphism in associations between PNMS and infant neural development and temperament, with girls appearing to be at elevated risk for profiles linked to anxiety and affective disorders. We hope these findings reinforce the importance of considering the role of the child's biological sex when designing and evaluating PNMS programming studies.

Acknowledgements K12 HS 022990: National Institutes of Health/Agency for Healthcare Research and Quality (SMB); T32 MH 018921-25: National Institutes of Health/National Institute of Mental Health (SS).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health of the Agency for Healthcare Research and Quality.

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- •• Of major importance

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