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ORIGINAL ARTICLE

Sex differences in early-life programming of the hypothalamic–pituitary–adrenal axis in humans suggest increased vulnerability in females: a systematic review

T. Carpenter, S. M. Grecian and R. M. Reynolds*

BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Fetal glucocorticoid overexposure is a key mechanism linking early development with later-life disease. In humans, low birth weight associates with increased fasting cortisol, hypothalamic–pituitary–adrenal (HPA) axis reactivity, and with cardiovascular risk and cognitive decline. As there are sex differences in these adult diseases, we hypothesized that there may be sex differences in programming of the HPA axis in response to prenatal stressors. We conducted a systematic review following Meta-Analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analysis. We searched Embase, MEDLINE and Web of Science from inception to 31 October 2016. We included studies related to sex differences, prenatal exposures and HPA axis. We excluded studies investigating specific disease states. The 23 included studies investigated the consequences of low birth weight, preterm birth and maternal stressors of asthma, psychosocial stress and glucocorticoid medications on HPA axis outcomes of placental glucocorticoid biology and offspring HPA axis function in early life and later life. Female offspring exposed to stressors had increased HPA axis reactivity compared with males. Furthermore, the female placenta increased its permeability to maternal glucocorticoids following maternal stress with changes in the expression of 11β-hydroxysteroid dehydrogenase enzymes in response to maternal glucocorticoid exposure or asthma. Among males there was some evidence of altered diurnal cortisol secretion. We conclude that although there is some evidence of male vulnerability leading to altered diurnal cortisol secretion, the female HPA axis is more vulnerable to programming, particularly in terms of its reactivity; this suggests a mechanism underlying sex differences in later-life diseases.

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Key words: human, HPA axis, sex differences

Introduction

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis has been proposed as a key mechanism underlying the link between early-life development and later-life disease.[1,2] Low birth weight, a surrogate marker of an adverse prenatal environment, is associated with higher fasting plasma cortisol,[3] increased reactivity of the HPA axis[4,5] and with cardiometabolic disease, mood disorders and accelerated cognitive decline.[2] A number of studies have suggested that there may be sex differences in this response, but to our knowledge there has been no systematic review to establish whether this finding is consistent across all published studies. This may be an important consideration in the aetiology of later-life diseases, including depression and cardiometabolic disease, which show marked sex differences in presentation and prevalence. This systematic review of published observational studies aimed to determine whether there were sex differences in the HPA axis responses to prenatal stress in humans. Specifically, we aimed to determine whether there were sex-specific differences in placental handling of glucocorticoid hormones and thus fetal glucocorticoid exposure and in HPA axis outcomes in the offspring at birth and across the lifespan.

Methods

Data sources

The Meta-Analysis of Observational Studies in Epidemiology guidelines were followed for conduct[6] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for reporting[7] of this systematic review. The literature search was conducted using Embase, MEDLINE and Web of Science from inception to 31 October 2016. The searches were limited to human studies and used terms as both keywords and indexing terms (Medical Subject Headings, MeSH) to identify studies related to sex differences, prenatal exposures and the HPA axis, for example, 'sex adj2 difference*', 'prenatal', 'cortisol' (for a full list, see Supplementary Table S1: 'Search Terms').

Study selection

All identified abstracts were screened for relevance by one reviewer (T.C.) and those that remained after screening were assessed by two reviewers (T.C. and S.M.G.) to establish whether they met the inclusion criteria. Any discrepancies in selection were discussed by all researchers until a consensus was reached.

*Address for correspondence: Professor R. Reynolds, BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, 47 Little France Crescent, Edinburgh EH16 4TJ, UK.
(Email r.reynolds@ed.ac.uk)

Studies were included if they investigated the prenatal environment, had a biological outcome that was related to the HPA axis (including placental handling of glucocorticoid hormones) and compared males and females. Studies were excluded if they investigated specific disease states where the disease does not reflect normal physiology (e.g. congenital adrenal hyperplasia, Cushing's disease). There were no exclusions related to study design.

Data extraction

Two independent reviewers (T.C. and S.M.G.) extracted relevant information on study design, characteristics, nature of prenatal exposure, methodology and outcome measures using a pre-specified data extraction form. Any disagreements were discussed and resolved by consensus.

Quality assessment

Studies were assessed for quality and risk of bias by the two reviewers (T.C. and S.M.G. or T.C. and R.M.R.) independently using a systematic scoring system[8] with objective criteria relating to the clarity of the research question, participant recruitment and retention, reliability of exposure and outcome measures, and consideration of confounding variables (Supplementary Table S2: 'Quality Scoring'). A paper could attain a rating of 'high', 'intermediate' or 'low' with 80, 60 or <60%, respectively, of the 14 applicable criteria being satisfied.

Data analysis and synthesis

Due to considerable heterogeneity in both clinical characteristics, study design and data, a descriptive synthesis of results was conducted. This included a description of the study design and sample studied, details of the prenatal exposure, biological outcome measurement and whether there were sex differences in this outcome. Studies were grouped according to whether they (a) measured changes in genes regulating fetal glucocorticoid exposure in the placenta or (b) investigated HPA axis outcomes in the offspring at birth or longer-term follow-up. For presentation purposes we grouped the prenatal environmental exposures into maternal asthma, inhaled corticosteroids, antenatal corticosteroids, preterm birth, low birth weight and other forms of antenatal stress (e.g. maternal cortisol, subjective stress, significant life events).

Results

Study design and participants

From 173 titles and abstracts, 39 full-text articles were assessed, of which 23 were included in the final data synthesis, including data on 3739 participants (Fig. 1). The studies included 12 prospective cohort studies, nine cross-sectional studies and two case–control studies, and were conducted in Europe ($n = 10$), Australia ($n = 7$), United States ($n = 3$), South America ($n = 2$) and the Philippines ($n = 1$). Sample characteristics are detailed in Table 1.

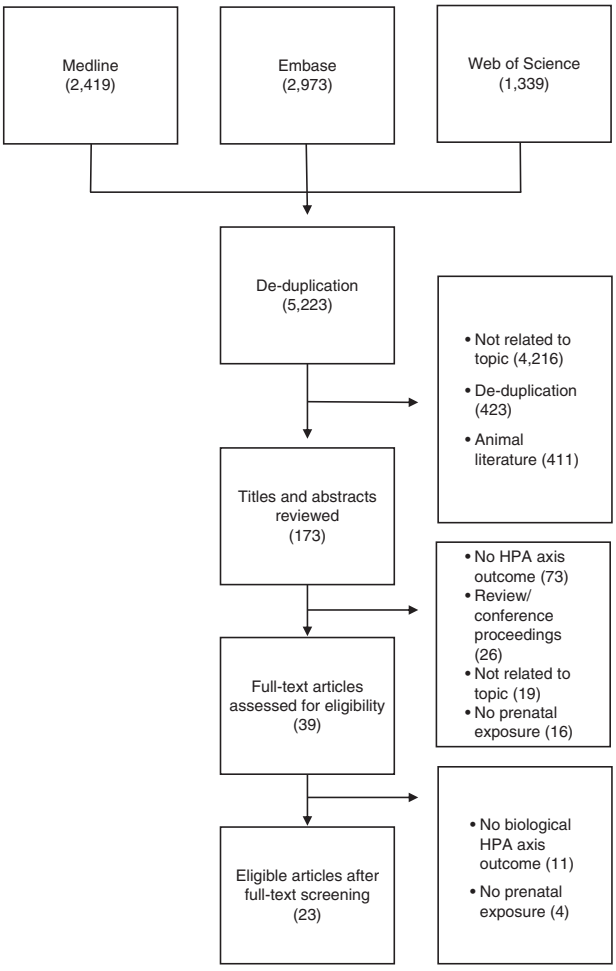

Fig. 1. Flow (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) diagram of included studies. HPA, hypothalamic–pituitary–adrenal.

Studies investigating sex differences in placental glucocorticoid handling

Eight studies investigated whether there were sex differences in genes regulating placental glucocorticoid handling and thus fetal glucocorticoid exposure (Table 2). The sample size varied from 43[16] to 244[20] placentas with exposures including maternal asthma, prenatal corticosteroids and preterm birth. Four studies investigated the effects of maternal glucocorticoid exposure on placental glucocorticoid receptor (GR) expression.[12,17,25,28] Studies that investigated maternal asthma as a stressor identified sex differences, with females showing a decrease in GR messenger RNA compared with males[17] and a different expression pattern of GR isoforms.[25] One study found no sex-specific effect of inhaled forms of corticosteroids, except that males in the treatment group and the control group showed a positive correlation between placental GR

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Table 1. *Descriptive table of all included articles*

Study	Year	Country	Study design	Sample characteristics
Ballard *et al.*[9]	1980	United States	Cross-sectional	36 neonates (22 male, 14 female)
Szathmari *et al.*[10]	2001	Hungary	Cross-sectional	70 young adults with low birth weight, mean age 20 years (37 male, 33 female), 30 controls with normal birth weight (14 male, 16 female)
Fall *et al.*[11]	2002	United Kingdom	Prospective cohort	83 healthy adults, 61–72 years (45 male, 38 female)
Murphy *et al.*[12]	2003	Australia	Prospective cohort	138 neonates from mothers with asthma (62 mild, 28 moderate, 48 severe[a]), 44 controls
Reynolds *et al.*[13]	2005	United Kingdom	Prospective cohort	311 adults, mean age 71 years (205 male, 106 female)
de Bruijn *et al.*[14]	2009	The Netherlands	Cross-sectional	103 children, 3–4 years (65 male, 67 female)
Mericq *et al.*[15]	2009	Chile	Cross-sectional	74 placentas (32 from females, 42 from males), 24 SGA, 25 AGA, 25 LGA
Stark *et al.*[16]	2009	Australia	Case–control	43 neonates and placentas (23 male, 20 female)
Hodyl *et al.*[17]	2010	Australia	Prospective cohort	122 neonates and placentas from mothers with asthma (52 mild, 71 moderate[b]), 51 controls; number of males and females not stated
Osei-Kumah *et al.*[18]	2011	Australia	Prospective cohort	49 placentas, 38 from mothers with asthma (23 treated with GC, 15 not treated with GC), 11 controls (22 male, 27 female)
Alexander *et al.*[19]	2012	Germany	Cross-sectional	209 children, 6–11 years (113 male, 96 female); 81 psychopathological pregnancies treated with GC, 43 psychopathological pregnancies not treated with GC, 85 controls
Demendi *et al.*[20]	2012	Hungary	Cross-sectional	244 placentas, 104 preterm and 140 term (122 male, 122 female)
Vedhara *et al.*[21]	2012	United Kingdom	Prospective cohort	139 adolescents, mean age 15 years (65 male, 74 female)
Hodyl *et al.*[22]	2013	Australia	Cross-sectional	53 placentas and neonates with threatened preterm labour 24–36 weeks (29 male, 24 female)
Lee *et al.*[23]	2014	Philippines	Prospective cohort	1403 young adults, 21–23 years (802 male, 601 female); 215 preterm, 1188 term
Quesada *et al.*[24]	2014	Brazil	Cross-sectional	61 children, 6–10 years (32 male, 29 female); 30 born preterm, 31 controls
Saif *et al.*[25]	2014	Australia	Prospective cohort	135 neonates and placentas (65 male, 70 female); 82 mothers with asthma, 53 controls
Gohlke *et al.*[26]	2015	Germany	Cross-sectional	54 children, 8–11 years (20 male, 34 female); 27 with birth weight <1000 g, 27 controls
Mina *et al.*[27]	2015	United Kingdom	Case–control	93 placentas (34 male, 69 female); 50 from severely obese mothers (BMI > 40), 43 from lean mothers (BMI < 25)
Saif *et al.*[28]	2015	Australia	Prospective cohort	111 placentas (55 male, 56 female); 26 preterm births treated with GC, 29 preterm births not treated with GC, 56 controls
Yong Ping *et al.*[29]	2015	United States	Prospective cohort	94 children, 2.5 years (46 male, 48 female), all exposed to prenatal maternal stress
Kaseva *et al.*[30]	2016	Finland	Prospective cohort	75 young adults, mean age 23.3 years (40 male, 35 female); 49 with very low birth weight, 36 controls
Ostlund *et al.*[31]	2016	United States	Prospective cohort	87 infants, mean age 19.8 weeks (42 male, 47 female); 41 with mothers who had a significant life event during pregnancy, 46 controls

SGA, small for gestational age; AGA, average size for gestational age; LGA, large for gestational age; GC, glucocorticoid medication, for example, betamethasone, dexamethasone; BMI, body mass index.

Articles ordered by year of publication.

[a]Asthma severity rated according to Australian Asthma Management guidelines.

[b]Asthma severity rated according to Asthma Control Questionnaire (taking into account night waking, morning asthma symptoms, activity limitation, shortness of breath, wheezing, short-acting β2-agonist use).[32]

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Table 2. *Studies assessing placental outcomes*

Study	Sample characteristics	Exposure	Outcome measure	Sex difference	Findings
Hodyl *et al.*[17]	mRNA analysis: 106 placentas (56 female, 60 male); 83 placentas from mothers with asthma, 33 controls	Maternal asthma	Placental GR mRNA	Sex difference	Decreased GR mRNA in females born to mothers with asthma (mild: 0.4 ± 0.35; moderate–severe: 0.75 ± 0.25), compared with control females [1.55 ± 0.4, $F(1,54) = 4.99$, $P = 0.003$]. No such change in GR mRNA expression in males *Data expressed as mean ± S.E.M. Data points estimated from graph*
Saif *et al.*[25]	135 neonates and placentas (65 male, 70 female); 82 mothers with asthma,[a] 53 controls	Maternal asthma	Placental GRβ expression	Sex difference	Increased cytoplasmic GRβ in male placentas of pregnancies complicated by mild asthma [control: 0.2 (0.16–0.6), $n = 24$; remission: 0.15 (0.05–0.2), $n = 3$; intermittent: 0.3 (0.12–1.7), $n = 21$; mild 0.5 (0.2–0.8), $n = 8$; moderate–severe: 0.3 (0.1–0.5), $n = 8$] *Data expressed as median (IQR)*
		Maternal asthma and inhaled corticosteroid use	Placental GRβ expression	Sex difference	Decreased placental nuclear expression of GRβ relative to cytoplasmic expression in females [0.33 (0–1.1) *v.* 0.2 (0–0.61), $P = 0.03$, $n = 15$] *Data expressed as median (IQR)*
Saif *et al.*[28]	111 placentas (55 male, 56 female); 26 preterm births treated with GC, 29 preterm births not treated with GC, 56 controls	Preterm birth	Placental GR expression	Sex difference	Increased cytoplasmic GRα isoform C expression in male preterm placentas relative to male term placentas [preterm: 0.20 (0–2.01); term: 0 (0–0.05), $P = 0.006$][b] Increased cytoplasmic GR A expression in male preterm placentas relative to male term placentas [preterm: 0.79 (0–12.64); term: 0 (0–0), $P = 0.01$] Increased nuclear GRα isoform C expression in female preterm placentas relative to term placentas [preterm: 0.19 (0–3.10); term: 0 (0–0.07), $P = 0.006$] *Data expressed as median (IQR)*
Murphy *et al.*[12]	138 neonates from mothers with asthma (62 mild, 28 moderate, 48 severe[c]), 44 controls	Maternal asthma, maternal glucocorticoid use	Placental 11β-HSD2 activity	Sex difference	Decreased placental 11β-HSD2 activity in females from pregnancies complicated by asthma whose mothers were not receiving glucocorticoid treatment (2.60 ± 0.33 nmol cortisone/mg protein/h, $n = 7$) compared with those receiving glucocorticoids (4.96 ± 1.02 nmol/mg/h, $n = 6$) and controls (6.88 ± 0.59 nmol/mg/h, $n = 26$, $P = 0.002$); no such difference in males Decreased placental 11β-HSD2 activity in placentas collected from males from pregnancies complicated by asthma whose mothers were receiving glucocorticoids compared with females from similar pregnancies ($P = 0.0016$) *Data expressed as mean ± S.E.M.*
Mericq *et al.*[15]	74 placentas (32 from females, 42 from males), 24 SGA, 25 AGA, 25 LGA	Reduced size for gestational age (SGA)	Placental 11β-HSD2 activity	Sex difference	Decreased placental 11β-HSD2 activity in female SGA placentas compared with male SGA placentas (female: 5.2 ± 0.9 pg/min/mg; male: 9.5 ± 1.0 pg/min/mg, $P = 0.007$) *Data expressed as mean ± S.E.M.*
Stark *et al.*[16]	43 neonates and placentas (23 male, 20 female)	Betamethasone administered either <72 h or >72 h before birth	Placental 11β-HSD2 activity	Sex difference	Increased placental 11β-HSD2 activity rate in females compared with males when betamethasone administered <72 h before delivery (female: 619.2 ± 70.8 nmol/mg/min; male: 313.4 ± 46.4 nmol/mg/min, $P < 0.01$) Increased placental 11β-HSD2 total activity in females compared with males when betamethasone administered <72 h before delivery (female: 334.2 ± 69.1 μmol/h; male: 121.3 ± 38.1 μmol/h, $P < 0.01$) *Data expressed as mean ± S.E.M.*
Demendi *et al.*[20]	244 placentas, 104 preterm and 140 term (122 male, 122 female)	Preterm birth	Placental 11β-HSD2 gene expression	No difference	Decreased placental 11β-HSD2 gene expression in preterm placentas compared with term [α value ± S.E. (α), −2.7 ± 0.83; lower confidence limit −1.87, upper confidence limit 0.11, $P = 0.05$]

Table 2. *Continued*

Study	Sample characteristics	Exposure	Outcome measure	Sex difference	Findings
					No difference in placental 11β-HSD2 gene expression between males and females born preterm [α value ± S.E. (α), −0.32 ± 0.55; lower confidence limit −0.83, upper confidence limit 1.02, $P = 0.05$]
Mina *et al.*[27]	93 placentas (34 male, 69 female); 50 from severely obese mothers (BMI > 40), 43 from lean mothers (BMI < 25)	Maternal serum cortisol	Placental 11β-HSD1 mRNA	Sex difference	Increased placental 11β-HSD1 mRNA levels in females where there was an increased maternal serum cortisol level (β = 0.46, $P \leqslant 0.05$) Decreased placental 11β-HSD1 mRNA levels in males where there was increased maternal serum cortisol (β = −0.48, $P \leqslant 0.05$)

mRNA, messenger RNA; GR, glucocorticoid receptor; SGA, small for gestational age; AGA, average size for gestational age; LGA, large for gestational age; GC, glucocorticoid medication; 11β-HSD, 11β-hydroxysteroid dehydrogenase; BMI, body mass index; IQR, interquartile range.
Articles ordered according to outcome axis measure (placental GR then 11β-HSD enzymes), then by year of publication.
[a] Asthma severity assessed by Juniper asthma questionnaire.[33]
[b] Data represented as median (IQR) relative protein expression.
[c] Asthma severity rated according to Australian Asthma Management guidelines.

heterogeneous nuclear RNA and cord blood cortisol, but that there was no such association where the mothers had untreated asthma or the offspring was female.[17] One study investigated the expression of GR isoforms in preterm birth, finding no sex differences in the total expression of GR apart from an increased level of GRα D2 in males.[28] It did however find differences in GR localization, with preterm male placentas showing higher cytoplasmic concentrations of GRα C and GRα A compared with full-term male placentas, with no such relationship in females.[28]

Four studies investigated effects on the expression and activity of 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes, with three of them finding a sex difference. With the exception of two studies, females showed changes that could lead to lower metabolism of cortisol by the placenta compared with males. This included reduced activity of placental 11β-HSD2 with maternal asthma[12] and prenatal corticosteroids, and with offspring reduced size for gestational age[15] as well as increased activity of 11β-HSD1 with increased maternal cortisol.[27] In contrast, one study found that 11β-HSD2 was increased in females following betamethasone exposure >72 h before delivery.[16] Another study found reduced placental 11β-HSD2 in both male and female preterm infants, with no sex difference.[20]

Studies investigating sex differences in HPA axis outcomes in the offspring

Cord blood cortisol concentrations

Six studies examined sex differences in umbilical cord blood cortisol concentrations with data from $n = 527$ participants and prenatal exposures of maternal asthma[12,17,25] and antenatal betamethasone for preterm birth[9,16,22] (Table 3). Two studies found evidence of sex differences, with higher umbilical blood cortisol in females whose mothers had moderate or severe asthma compared with mild asthma[17] and whose mothers were treated with betamethasone <72 h before delivery.[16] Two studies with maternal asthma[12,25] and two with betamethasone[9,22] found no sex differences in cord cortisol concentrations.

Static HPA axis measures

Five studies investigated plasma/serum cortisol concentrations (either in the morning or diurnal profiles), three with low birth weight[10,11,30], and two with preterm birth[23,24], as the exposure (Table 3). The age at follow-up varied from 5 months to 72 years. One found that in childhood females born preterm had higher morning salivary cortisol than full-term females, as well as preterm and full-term males.[24] One study in young adults found no difference in cortisol awakening response or diurnal cortisol secretion between individuals with very low birth weight and controls, with no sex differences.[30] Another study in young adults found that males with preterm birth had decreased waking cortisol compared with males with term birth, and a shallower slope of diurnal cortisol decline, but found no such relationships among females.[23] In contrast, a study in older

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Table 3. *Offspring outcomes*

Study	Sample characteristics	Exposure	HPA axis measure	Sex difference	Findings (mean cortisol in nmol/l, unless otherwise specified)
Ballard *et al.*[9]	36 neonates (22 male, 14 female)	Betamethasone for premature birth	Cord cortisol	No difference	No difference between male and female cord cortisol concentration, regardless of timing of betamethasone administration [male: 380 (S.E.: 250); female: 390 (S.E.: 190)]
Murphy *et al.*[12]	138 neonates and placentas from mothers with asthma (62 mild, 28 moderate, 48 severe[a]), 44 controls	Maternal asthma	Umbilical vein cortisol	No difference/ difference not tested	Umbilical cortisol concentrations not significantly different between female control (214.2 ± 20.2), asthma without glucocorticoid group (279.8 ± 56.3) or asthma with glucocorticoid group (224.2 ± 22.9, Kruskal–Wallis ANOVA, $P = 0.881$) Umbilical cortisol concentrations not significantly different between male control (193.2 ± 27.7), asthma without glucocorticoid group (287.8 ± 59.6) or asthma with glucocorticoid group (281.4 ± 41.8, Kruskal–Wallis ANOVA, $P = 0.624$) *Data expressed as mean ± S.E.M.* Statistics for comparison between sexes not stated
Stark *et al.*[16]	43 neonates and placentas (23 male, 20 female)	Betamethasone for premature birth, administered <72 h or >72 h before delivery	Umbilical artery cortisol	Sex difference	Increased female umbilical artery cortisol (190 ± 70) compared with male (50 ± 15) when betamethasone administered <72 h before delivery [$F(1,26) = 7.59$, $P = 0.01$]. No difference when administered >72 h before delivery ($P = 0.14$)
			Day 1 neonatal urinary cortisol (log nmol/l: mmol/l of creatinine)	Sex difference	Significant interaction between antenatal steroid exposure, sex and perinatal stress [$F(1,38) = 4.23$, $P = 0.04$]. Increased female day 1 urinary cortisol (3.85 ± 0.45) compared with male (1.8 ± 0.45, $P < 0.01$) when betamethasone administered <72 h before delivery. No difference when administered >72 h before delivery *Data expressed as mean ± S.E.M. Data points estimated from graph*
Hodyl *et al.*[17]	122 neonates and placentas from mothers with asthma (52 mild, 71 moderate[b]), 51 controls; number of males and females not stated	Maternal asthma	Cord cortisol	Sex difference	Increased female fetal cord cortisol with maternal moderate–severe asthma when compared against mild asthma or control [$F(2,67) = 3.2$, $P = 0.047$]. No such difference in males
Hodyl *et al.*[22]	53 placentas and neonates with threatened preterm labour 24–36 weeks (29 male, 24 female)	Betamethasone for premature birth, administered <72 h or >72 h before delivery	Cord cortisol	No difference	No difference between male and female cord cortisol levels, regardless of timing of betamethasone administration [female, <72 h: 35.9 (11.4–56.1) *v.* >72 h: 21.25 (13.5–35); male, <72 h: 21.2 (16.2–42.1) *v.* >72 h: 27.9 (22.6–53.7), *P*-value not stated] *Data reported as: median (25th–75th percentile). Cortisol in ng/ml*

Table 3. *Continued*

Study	Sample characteristics	Exposure	HPA axis measure	Sex difference	Findings (mean cortisol in nmol/l, unless otherwise specified)
Saif *et al.*[25]	135 neonates and placentas (65 male, 70 female); 82 mothers with asthma, 553 controls	Maternal asthma	Cord cortisol	Evidence of difference inconclusive	Decreased male cord cortisol with maternal asthma compared with controls; no such finding in females. Male with maternal asthma: 1.72 (S.E.M.: 0.1), control: 2.7 (S.E.M.: 0.4); female with maternal asthma: 1.9 (S.E.M.: 0.09), control 1.8 (S.E.M.: 0.19), *P*-value not stated
Ostlund *et al.*[31]	87 infants, mean age 19.8 weeks (42 male, 47 female); 41 with mothers who had a significant life event during pregnancy, 46 controls	Maternal SLE	Glucocorticoid receptor gene (*NR3C1*) methylation	Trend towards sex difference	Increased methylation of *NR3C1* in females whose mother had experienced an SLE during pregnancy (2.38, S.D. = 0.99) compared with controls (1.85, S.D. = 0.41), $t(21,41) = -2.01$, $P = 0.057$. No such trend in males: $t(33) = -0.20$, $P = 0.84$
Gohlke *et al.*[26]	54 children, 8–11 years (20 male, 34 female); 27 with birth weight <1000 g, 27 controls	ELBW (<1000 g)	Urinary steroid metabolites	Sex difference not tested	Increased mean cortisol production in ELBW boys and girls compared with controls. ELBW boys: 12,400 μg/l, control boys: 6738 μg/l, $P = 0.05$. ELBW girls: 10,717 μg/l, control girls: 6200 μg/l, $P = 0.007$
Szathmari *et al.*[10]	70 young adults with low birth weight (900–2500 g), mean age 20 years (37 male, 33 female), 30 controls with normal birth weight (14 male, 16 female)	Low birth weight	Morning serum cortisol, 7:30 am	No difference	Females with low birth weight: 250 (S.D.: 70) Males with low birth weight: 270 (S.D.: 60) Statistics for comparison not stated
Lee *et al.*[23]	1403 young adults, 21–23 years (802 male, 601 female); 215 preterm, 1188 term	Preterm birth	Diurnal salivary cortisol profiles	Sex difference	Decreased waking cortisol in males with preterm birth compared with males with term birth. Term mean: 7.2 mmol/l (S.D.: 4.5); preterm mean 6.4 mmol/l (S.D.: 3.3), $P < 0.05$ No significant differences in cortisol in females with preterm birth compared with females with term birth. Waking cortisol, term mean: 7.8 mmol/l (S.D.: 3.8); preterm mean: 7.7 mmol/l (S.D.: 3.9) Slope of diurnal cortisol decline shallower in preterm males, than term males. Term: −0.32 (S.D.: 0.31) mmol/l/h; preterm: −0.26 (S.D.: 0.26) mmol/l/h, $P < 0.05$ No significant difference in slope of diurnal cortisol decline in preterm females compared with term females. Term: −0.37 (S.D.: 0.25) mmol/l/h; preterm: −0.35 (S.D.: 0.26) mmol/l/h
Fall *et al.*[11]	83 healthy adults, 61–72 years (45 male, 38 female)	Low birth weight	Morning serum cortisol, 7:30–9:00 am	Evidence of difference inconclusive	Male: 444.8 (birth weight tertile 1), 410.2, 407.8 (birth weight tertiles 2 and 3); combined S.D.: 90.1 Female: 345.1 (birth weight tertile 1) *v.* 297.0, 307.5 (birth weight tertiles 2 and 3); combined S.D.: 79.4 Statistics for comparison not stated
Yong Ping *et al.*[29]	94 children, 2.5 years (46 male, 48 female), all exposed to prenatal stress	Prenatal maternal stress (Iowa flood of 2008)	Salivary cortisol following mother–child separation stressor	Sex difference	Increased cortisol after stressor in females, no such effect in males. Female cortisol increase 20 min post-stressor: $t(40) = -2.019$, $P < 0.05$; 45 min post-

					stressor: $t(42) = -2.386$, $P < 0.05$. Data for males not reported Increased salivary cortisol after 45 min in females whose mothers reported greater subjective stress during pregnancy ($y = 0.0464x - 0.0014$, $P < 0.05$); no such effect in males ($y = 0.0179x + 0.0377$, $P =$ not significant). Increased area under the curve for cortisol after 45 min whose mothers reported greater subjective stress during pregnancy ($y = 0.0483x - 0.0721$, $P < 0.05$); no such effect in males ($y = -0.0108x + 0.0163$; $P =$ not significant)
de Bruijn *et al.*[14]	103 children, 3–4 years (65 male, 67 female)	Prenatal maternal anxiety or affective complaints (scoring >1 S.D. over the mean on three separate prenatal anxiety and depression assessments)	Log score of salivary cortisol concentrations at the start of a home visit (T1), after a mother–child interaction task (T2) and after a potentially frustrating task (T3)	No difference	Male: T1, 0.37 (S.D.: 0.29); T2, 0.21 (S.D.: 0.22); T3, 0.17 (S.D.: 0.25) Female: T1, 0.60 (S.D.: 0.42); T2, 0.39 (S.D.: 0.29); T3, 0.30 (S.D.: 0.23)
Quesada *et al.*[24]	61 children, 6–10 years (32 male, 29 female); 30 born preterm, 31 controls	Preterm birth	Awakening salivary cortisol	Sex difference	Higher awakening cortisol in preterm females (15.5, S.E.M.: 1.0) than full-term females (10.6, S.E.M.: 0.9, $P = 0.040$), preterm males (11.0, S.E.M.: 0.9) and full-term males (10.1, S.E.M.: 0.9, *P*-value not stated)
			Peak salivary cortisol concentrations following Trier Social Stress Test (children)	Sex difference	Higher peak cortisol in preterm females (18.2, S.E.M.: 2.7) than full-term females (6.0, S.E.M.: 2.4, $P < 0.01$), preterm males (8.5, S.E.M.: 2.4) and full-term males (7.0, S.E.M.: 2.5, *P*-value not stated)
Alexander *et al.*[19]	209 children, 6–11 years (113 male, 96 female); 81 psychopathological pregnancies treated with GC (PP/GC), 43 psychopathological pregnancies not treated with GC, 85 controls	Course of dexamethasone/ betamethasone in mothers admitted for complications; psychopathological pregnancy	Peak salivary cortisol concentrations following Trier Social Stress Test (children)	Sex difference	Where mothers had psychopathological pregnancy, higher peak cortisol in females prenatally treated with GC than males prenatally treated with GC. Female PP/GC: 14.166 (95% CI 11.354, 16.977); male PP/GC: 9.256 (95% CI 7.436, 11.076), $P < 0.05$
Vedhara *et al.*[21]	139 adolescents, mean age 15 years (65 male, 74 female)	Prenatal maternal depression	Log score of peak salivary cortisol following 35% CO_2 stress test	No difference	Female: −0.14 (95% CI −0.31, 0.04) Male: −0.14 (95% CI −0.27, −0.01)
Kaseva *et al.*[30]	75 young adults, mean age 23.3 years (40 male, 35 female); 49 with VLBW, 36 controls	VLBW (<1500 g)	Log score of cortisol awakening response	No difference	No difference in cortisol awakening response between VLBW (2.0, S.D.: 1.9) and control groups (2.0, S.D.: 1.9, $P = 0.85$); no sex differences (test not reported)
			Log score of diurnal cortisol secretion	No difference	No difference in daily salivary cortisol between VLBW males and male controls [8.8% (95% CI −31.3, 72.2), $P = 0.71$] or females and female controls [18.8% (95% CI −11.8, 60.0), $P = 0.25$]
			Log score of cortisol following dexamethasone suppression test	No difference	No difference in daily salivary cortisol following low-dose dexamethasone between VLBW males and male controls [−16.7% (95% CI −68.3, 118.6), $P = 0.7$] or females and female controls [−9.7% (95% CI −49.9, 139.9), $P = 0.81$]

Table 3. *Continued*

Study	Sample characteristics	Exposure	HPA axis measure	Sex difference	Findings (mean cortisol in nmol/l, unless otherwise specified)
Reynolds *et al.*[13]	311 adults, mean age 71 years (205 male, 106 female)	Low birth weight	Increase in peak plasma cortisol concentrations following ACTH administration per 1 lb decrease in birth weight	No difference	Male: 12.6 (95% CI 1.4, 23.8) Female: 14.8 (95% CI −0.4, 29.9)

HPA, hypothalamic–pituitary–adrenal; SLE, significant life event; ELBW, extremely low birth weight; GC, glucocorticoid medication, for example, betamethasone, dexamethasone; VLBW, very low birth weight; ACTH, adrenocorticotropic hormone; CI, confidence interval; .

Articles ordered according to HPA axis measure (static then dynamic), then by age at follow-up, then by year of publication. Where an article refers to both static and dynamic HPA axis measures, it is placed with the others that refer to dynamic measures.

[a]Asthma severity rated according to Australian Asthma Management guidelines.

[b]Asthma severity rated according to Asthma Control Questionnaire (taking into account night waking, morning asthma symptoms, activity limitation, shortness of breath, wheezing, short-acting β2-agonist use).[32]

adults[11] found higher morning serum cortisol concentrations in males and females of low birth weight than in males and females of higher birth weight but no formal statistical comparison was conducted. Two studies found increased morning salivary or serum cortisol in offspring exposed to neonatal corticosteroids or low birth weight, but found no sex differences in this effect either in early adulthood[10] or adolescence.[34] Another study investigated urinary steroid metabolites in extremely low birth weight children, with extremely low birth weight males and females having increased cortisol production compared with controls, but did not test whether there was any sex difference.[26] A study investigating GR gene methylation in DNA extracted from buccal cells collected in infancy found that females whose mothers had experienced a significant life event during pregnancy had increased methylation of *NR3C1* compared with control females, finding no such relationship in males.[31]

Dynamic HPA axis measures

Six studies used a stress challenge to attempt to elicit differences in HPA axis reactivity (Table 3). Two used versions of the Trier Social Stress Test (TSST) were conducted in children and adolescents.[19,24,34] Although the prenatal exposure differed (preterm birth;[24] antenatal glucocorticoids[19]), both found a sex difference in HPA responses with a greater response in peak salivary cortisol in females. Two studies used other stress-inducing tasks. One study among toddlers involved a brief period of separation from the child's mother and found that females had an increase in post-stressor cortisol and males did not, as well as a greater increase in cortisol in females whose mothers reported greater subjective stress during pregnancy, with no such correlation in males.[29] Another study[14] used a different stress-inducing task with 4-year-old children (confronting the child with a transparent box from which it was impossible to extract a toy), and found no difference in cortisol between males and females who had been exposed to prenatal maternal anxiety. One study used a physiological stressor – a breath of 35% inhaled CO_2 gas – in offspring exposed to maternal depression and found no sex differences in peak salivary cortisol.[21]

Neither of the studies testing HPA axis reactivity or central negative feedback [by adrenocorticotropic hormone (ACTH) stimulation or dexamethasone suppression, respectively] found sex differences in HPA axis responses to exposures of low birth weight[13] or very low birth weight.[30]

Quality assessment

Most studies were determined to be of intermediate quality, scoring 60–80%, with three being classified as low quality, scoring under 60%. Studies scored as low quality either did not statistically adjust for confounding variables, did not report loss to follow-up, reported a loss to follow-up rate of over 20% or did not assess exposures more than once over time where it would have been applicable (Supplementary Table S2: 'Quality Assessment').

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Discussion

This systematic review including 23 studies and data on $n = 3739$ participants showed evidence of sex differences in HPA responses to prenatal stressors with increased vulnerability of the female HPA axis at a number of different levels and in response to a number of different prenatal stressors.

The placenta plays a key role in regulating fetal glucocorticoid exposure through the activity of the enzymes such as 11β-HSD2, which deactivates cortisol; 11β-HSD1, which regenerates cortisol; and the levels of GR, which signal glucocorticoid sensitivity. Overall, the findings suggested that in comparison with males, the female placenta increases its permeability to maternal glucocorticoids following maternal stress. This occurred through sex-specific lower expression of 11β-HSD2[12] or increased expression of 11β-HSD1[27] and by changes in GR expression and localization,[17,25,28] consistent with increased female fetal exposure to glucocorticoids. Having said this, one relatively large study that examined the association with preterm birth found a reduction in 11β-HSD2 in both sexes, with no sex difference,[20,35] suggesting that in preterm birth at least, the nature of any sex difference is more complex. However, it may be the case that a dysfunctional placental 11β-HSD2 barrier is a causative factor in preterm birth itself,[20,35] and thus it is to be expected that preterm infants of both sexes show reduced placental 11β-HSD2.

When examining sex differences in HPA axis outcomes in the offspring, we identified studies using cord blood as an early measure of the infant HPA axis, and a number of studies measuring HPA axis activity in children and adults using both static and dynamic measures. Data on cord cortisol concentrations are difficult to interpret as they may represent either the basal level of secretion in the fetal HPA axis, the HPA axis response of the fetus to the stress of birth or short-term suppression of the fetal HPA axis by glucocorticoid medications. Two of the six identified studies[16,17] reported higher cortisol concentrations in blood measured in female offspring, consistent with increased fetal glucocorticoid exposure in females. Findings from later in life were also not consistent. Studies on diurnal cortisol secretion either did not find a sex difference,[10,26,30] found altered secretion in males[23] or in females.[24] Although the findings of HPA axis measures in the studies conducted in children and adults were not consistent, the only sex difference in HPA axis reactivity reported was consistent with increased reactivity in females.[19,24,29] Of note, both of these studies were conducted using the TSST[19,24] and a maternal separation event,[29] whereas other stress tests and hormone challenges failed to show any sex differences.[13,14,21,30] The absence of findings from dexamethasone or ACTH administration suggests that the mechanism of sex-specific programming may be to do with higher neural inputs into the HPA axis rather than its sensitivity to its own components. However, one study suggested that sensitivity of the female physiology in general to glucocorticoids may be increased in situations of maternal stress.[31]

We included a broad definition of prenatal stressors including maternal inflammation, pharmacological intervention, psychological stressors and low birth weight/preterm birth. Low birth weight and preterm birth are considered the outcome of growth-restricting stressors during pregnancy and small for gestational age was associated with reduced activity of prenatal 11β-HSD2 and increased activity of 11β-HSD1 in females. These changes would allow the delivery of more maternal cortisol to the fetus, and may indeed be a pathway contributing to growth restriction. Females with low birth weight or preterm birth had higher morning cortisol in one study,[24] but not all.[10,11,23,30] There was also evidence that females born preterm had increased HPA axis reactivity to stressful stimuli.[24] Whether these changes are a cause or consequence of preterm birth is unknown. Nevertheless, if low birth weight and preterm birth are considered as a marker of prenatal stress, these findings support the argument that females are more vulnerable to the programming effects of prenatal stress in terms of HPA axis reactivity, possibly not in terms of diurnal secretion.

A number of studies considered maternal asthma as a prenatal stressor. Maternal asthma was found to decrease the placental barrier to glucocorticoids in terms of 11β-HSD2[12] and, putatively, GR.[17,25] In one study, treatment of asthma with inhaled betamethasone ameliorated the effect,[12] which suggests that it is the presence of the asthma itself rather than any associated factors in lifestyle or treatment that is responsible for the programming. However, it is possible that factors relating to treatment administration and compliance confound these results. No studies examined the association between maternal asthma and offspring later-life HPA axis outcomes, though these might be anticipated due to the observed alteration of the placental glucocorticoid barrier. A large follow-up study of clinical outcomes of offspring exposed to asthma *in utero* also did not examine whether there were sex differences in outcomes.[36]

Although use of prenatal glucocorticoids was associated with increased activity of placental 11β-HSD2 in females, it was also associated with an increase in cord blood cortisol in females when given within 72 h of delivery.[16] Prenatal glucocorticoids were also associated with differential later-life outcomes, with females showing greater HPA axis reactivity to stress in terms of cortisol release.[19] Overall, glucocorticoid medication appeared to induce offspring, although not placental, changes that were similar to those observed with inflammatory stress and low birth weight.

Our review identified studies investigating a variety of psychological stressors including maternal mood,[21] emotional complaints,[14] subjective stress[29] and presence of psychopathology,[19] but sex differences in the offspring HPA axis were only apparent in one study.[29] This suggests that either the psychological measures studied were not severe enough to reliably induce a programming effect or that a biological/hormonal response to stress – or its pharmacological mimic – is required to induce sex-specific prenatal programming. The one study that found a sex difference[29] investigated mothers who had all been affected by a single major stressor – the Iowa flood of 2008 – suggesting that other studies investigated stressors whose nature was too broad, or not sufficiently severe.

No studies investigated the association between maternal psychological measures and placental outcomes.

Mechanisms of the sex differences in the HPA axis responses to stress are unknown, but it is conceivable that they exist to effect the vulnerability–viability trade-off that is made by male and female fetuses in response to stress. It has been observed that males exposed to early environmental adversity suffer a risk to their viability. Although females suffer no such cost to their viability, they show increased vulnerability to adversity later in life.[37]

A strength of our study is that a systematic and comprehensive review process, devised with an experienced librarian, reported in line with PRISMA guidelines, was followed for this review. Two reviewers independently assessed eligibility of the titles, abstracts and full-text studies. Studies only including specific clinical populations with altered HPA physiology, for example, congenital adrenal hyperplasia, were excluded to ensure that our results were generalizable to the general population. However, there are some potential limitations to our study. The search terms were broad, and it is possible we have missed some potentially eligible studies. The studies were heterogeneous in terms of size, countries, ethnicities, age groups, methodology and reporting of statistical analysis. Most studies were graded as intermediate quality because they did not report sample size justification, participation rate of eligible persons, experimenter blinding or loss to follow-up.

In conclusion, although there was heterogeneity in study type and the nature of the findings, this systematic review demonstrated some evidence of increased programmed vulnerability to maternal stressors of the HPA axis in females compared with males, particularly in terms of HPA axis reactivity. Although there is evidence that males are not unaffected, any effect appears to be manifested in altered diurnal cortisol secretion. The limited evidence from diverse, moderate quality studies suggests that further research is required in order to determine whether this is a mechanism underlying differences in later-life diseases.

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Conflicts of Interest

None.

Supplementary material

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