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Prenatal stress and later metabolic consequences: Systematic review and meta-analysis in rodents

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ABSTRACT

Background: Numerous rodent studies have evaluated the effects of maternal stress (MS) on later in life susceptibility to Metabolic Syndrome (MetS) intermediate phenotypes with varying results. The aim of this study was to quantitatively synthesize the available data on the effects of MS on offspring obesity, estimated indirectly by body mass (BM), body fat (BF) and plasma leptin; systolic blood pressure (SBP); plasma glucose (and insulin) and blood lipid concentrations.

Methods: Literature was screened and summary estimates of the effect of MS outcomes were calculated by using random-effects models. Data on the effects of exogenous corticosteroid administration (or inhibition of 11β-HSD2) during pregnancy in rodents was analysed separately to characterize the direct phenotypic effects of prenatal corticosteroid excess (PCE).

Results: We conducted 14 separate meta-analyses and synthesized relevant data on outcomes scarcely reported in literature. Both MS and PCE were associated with low birth weight without rapid catch-up growth resulting in decreased body mass later in life. Our analysis also revealed significant and contradictory effects on offspring adiposity. Little evidence was found for effects on glucose metabolism and blood lipids. We identified increased SBP in offspring exposed to PCE; however, there is not enough data to draw any conclusion about effects of MS on SBP.

Conclusions: Neonatal weight proved to be decreased in offspring prenatally exposed to stress or corticosteroids, but laboratory rodents in the absence of a challenging environment did not show catch-up growth. The available evidence is inconclusive regarding the effect on adiposity revealing clear methodological and knowledge gaps. This meta-analysis also confirmed a significant positive association between PCE and SBP. Nevertheless, additional studies should address the association with MS.

1. Introduction

The experience of acute intense physical or emotional stress or chronic stress, may trigger or exacerbate several psychological and biological conditions, including anxiety disorders, depression, obesity, and metabolic syndrome (MetS) (Farr et al., 2014; Pervanidou and Chrousos, 2012). In-utero exposure to maternal stress (MS) proved to increase short- and long-term risk of negative cognitive and physiological health consequences (Entringer et al., 2015). In rodents, different studies have reported effects on metabolic offspring health (Cao-Lei et al., 2017), albeit with varying results.

The role of maternal health during pregnancy in shaping the health of the offspring has long been recognized. The Developmental Origins of Health and Disease hypothesis, also called "foetal programming", can be defined as the response to a specific challenge during a critical developmental time period that changes the trajectory of development with long-lasting alterations in the structure and function of foetal organs (Zambrano et al., 2016).

Since the first description by Barker and co-workers of the foetal metabolic programming of adult chronic diseases, there has been considerable epidemiological evidence for a strong association between intrauterine growth retardation and low birth weight

Abbreviations: BF, body fat; BM, body mass; BW, birth weight; HDL-C, high density lipoprotein cholesterol; LBW, low birth weight; MS, maternal stress during pregnancy; MetS, Metabolic Syndrome; PCE, prenatal corticosteroid excess; SBP, systolic blood pressure.

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(LBW) and adverse cardio-metabolic outcomes in adult life (Barker, 2004; Eriksson, 2005). Though LBW per se may not be the cause of disease, it suggests that permanent adaptations to a suboptimal environment during foetal life are at work (Harris and Seckl, 2011). Previous meta-analyses described a significant but low-level inverse relation between stress experienced by a woman during pregnancy and BW (Bussières et al., 2015; Littleton et al., 2010). In order to better understand the contribution of MS and considering the obvious difficulties inherent to human research in this field, different animal models of MS have been developed (Jaggi et al., 2011). Evidence in rodents showed that changes to the intrauterine environment, caused by stress of the mother during pregnancy may modify BW.

Stress is a state of real or perceived threatened homeostasis, associated with the activation of the "stress system", mainly comprised by the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Sympathetic Nervous System (Pervanidou and Chrousos, 2012). Exposure to stressful events leads to an increased release of glucocorticoids by activation of the HPA axis (Krolow et al., 2013). Several mechanisms have been postulated to account for the relation between MS and birth outcome (Beijers et al., 2014). Programming of the HPA axis has emerged as a key underlying mechanism (Cao-Lei et al., 2017). A previous meta-analysis has found that prenatal corticosteroid exposure (PCE) for women at risk of preterm birth was associated with a reduction in BW (Crowther et al., 2015). There is growing interest in the role of glucocorticoids as a common underlying mechanism mediating the effects of intrauterine growth restriction and the programming of poor health outcomes in later life, i.e. hypertension (Woods and Weeks, 2005; Woods, 2006), obesity and diabetes (Reynolds, 2010).

We hypothesized that there is a link between MS and the adverse intrauterine environment predisposing to LBW and associated metabolic alterations later in life. Our first aim was to quantify the overall short-term effects of MS (or PCE) on offspring's BW in rodents. Subgroup analysis and meta-regression were run to evaluate the influence of biological (species and sex) and experimental factors (timing of maternal manipulation and stress model). We further reviewed the influence of additional moderators: maternal BM and litter size. Meta-analyses on the effects of MS and the effects of exogenous corticosteroid administration (or inhibition of 11β-HSD2) during pregnancy in rodents were performed separately to characterize the direct phenotypic effects of corticosteroids on the foetus.

Our second aim was to quantify the overall effect of MS (or PCE) on offspring's MetS related phenotypes. We collected the experimental data available on rodents for the long-term effects of MS on obesity, estimated indirectly by body mass (BM), body fat (BF) and plasma leptin; systolic blood pressure (SBP); plasma glucose (and insulin) and lipid concentrations. We assessed the long-term programming effects collecting data on phenotypes at different time points after birth.

2. Methods

2.1. Search strategy

Systematic literature search was performed following guidelines outlined in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher et al., 2009). A review protocol was strictly followed and a PRISMA checklist is included in Supplementary information (SI) 1 for further details. We searched for published studies on PubMed database and additionally obtained the citations of relevant articles by reviewing the references of retrieved studies and review articles. The literature search was done on articles published up to March 18th, 2019 using the following MeSH and text keywords: (stress OR glucocorticoids OR corticosterone OR betamethasone OR dexamethasone OR carbenoxolone) AND (maternal OR mother OR prenatal OR antenatal OR perinatal OR programming OR pregnancy OR dam OR mate OR breeding) AND ("body weight" OR "body mass" OR "birth weight" OR "adipose tissue" OR "fat weight" OR "adipose weight" OR "gonadal fat" OR "retroperitoneal fat" OR "abdominal fat" OR "mesenteric fat" OR adiposity OR glucose OR insulin OR leptin OR lipid OR cholesterol OR triglycerides OR triacylglyceride OR pressure OR "blood pressure" OR "arterial tension") AND (mice OR mouse OR murine OR rat OR rats OR rodents) AND (offspring OR pups).

2.2. Inclusion and exclusion criteria

Retrieved articles were screened to identify experimental studies on rodents (mouse, rat, hamster and/or guinea pig) where dams were subjected to a stressor or exposed to exogenous corticosteroids (or inhibition of 11β-HSD2) around gestation time, and phenotypes were measured in offspring. Eligible outcomes included: BW, BM, BF, leptin, SBP, glucose, insulin, triglycerides and High Density Lipoprotein Cholesterol (HDL-C). We further screened articles using the following inclusion criteria: 1) the experiment was performed on non-mutant animals; 2) experimental dams were stressed before or during pregnancy and a control group was available; 3) dams and offspring of both control and stressed dams were not exposed to further intervention or to invasive procedures, such as surgery, that may have required anaesthesia or fasting, or additional drug, alcohol, diet, exercise or other possible confounding interventions prior to or during the experiment. Exceptions were animals exposed to injections with vehicle or gavage, as long as both control and experimental groups were exposed. Research articles were eligible if they studied the effects of any type of acute/chronic maternal stress such as physical stress (e.g. immobilization/restraint), psychological stress (e.g. sleep deprivation) or variable/unpredictable stress. Studies of other unrelated hostile conditions during pregnancy such as biological stress (infection/sepsis, hypoxia/ischemia), nutritional stress (e.g. nutrient restriction/deprivation, e.g. protein restriction), or exposure to chemicals/pesticides were excluded. Searches were restricted to reports published in English. After screening of titles and abstracts, two reviewers independently examined full text articles. Disagreements were resolved in consensus discussions. Unpublished data of our group was also included.

2.3. Data collection and data analysis

Data collection is described in SI 3. We performed the analyses independently for each outcome as previously described (Tellechea et al., 2017). Effect size (standardized mean difference, d) and confidence intervals were calculated. Summary estimates were calculated using random-effects models. Where a standard error was presented, the value was converted to a standard deviation. To test robustness of the estimates, we performed sensitivity analyses by omitting one study at a time and calculating the pooled effect size for the remainder of the studies. Heterogeneity was evaluated with the Q statistic and I-squared statistic. Measures of heterogeneity of 25 %, 50 % and 75 % were considered low, moderate and high, respectively (Higgins et al., 2003). We use subgroup analysis to explore heterogeneity and to investigate the contribution of specific factors to heterogeneity (for this test a p-value of less than 0.1 indicates a statistically significant subgroup effect). Moderators were: offspring sex, species, offspring age stage, exposure period, intervention span, stress model or administered drug (when applicable), and maternal BM. Meta-regression was used to uncover the potential influence of the following covariates: offspring age at testing (in days), exposure duration, weaning day, litter size (before culling), quality score (unpublished studies excluded) and year of publication (unpublished studies ex-

cluded). Ocular inspection of each scatterplot was performed to verify the presence of possible outliers. Further sensitivity analyses were conducted to observe the impact of removing studies at risk of bias. Subset Dataset 2 was obtained by strictly excluding studies were control animals were injected with vehicle, received vehicle in drinking water, or were pair fed (food restriction is considered a stressor). We also excluded studies were: dams were exposed to other manipulations as gavage or injections, delivery did not occur naturally, or offspring were exposed to injections with vehicle (saline, DMSO, or oil). Finally, subset Dataset 3 only included studies were offspring were cross-fostered to non-stressed dams. Subgroup analysis was not performed in Dataset 2 or 3. To check for publication bias we used the Egger's test and visual inspection of funnel plots for the presence of data distribution asymmetry. Calculations were performed using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA). A p-value <0.05 was considered to be statistically significant unless otherwise stated.

2.4. Selection of included studies

Literature search is summarized in the PRISMA diagram presented in Fig. 1. The list of excluded studies with reasons for exclusion is shown in SI 3.

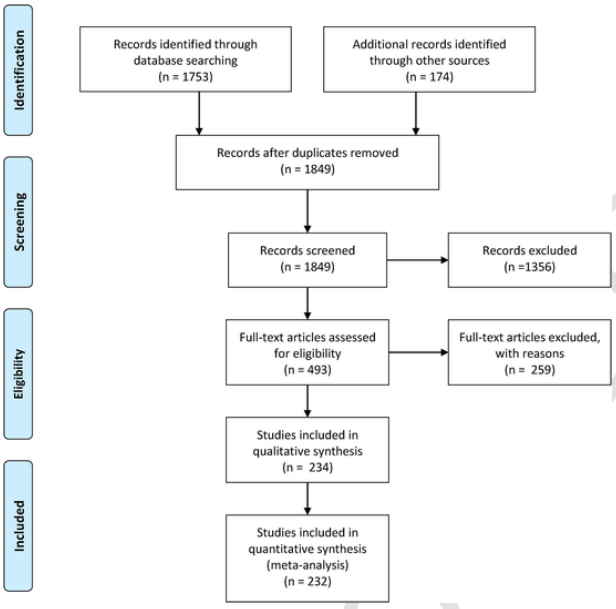

Fig. 1. PRISMA flow chart summarizing study selection processes.

3. Results

3.1. Systematic review and meta-analyses on maternal stress

3.1.1. Characteristics of included studies

120 citations were used in meta-analyses (References are available at SI 4.1) and recent data of our group was also included (Juarez YR unpublished, methods available at SI 4.2). Study characteristics are shown in SI 4.3. Most studies used rats and outcomes were reported either for males, females or mixed-sex groups. Data on timing of maternal manipulations for each outcome is presented in SI 5.1. In all cases animals had reached sexual maturity at the time of beginning the stress. In most studies, focus has been on the third trimester of gestation (upper third of gestation) when the embryo is undergoing the greatest period of growth. Characteristics of MS procedures are shown in SI 6.1. We performed seven separate meta-analyses on the relationship between MS and outcomes under study: BW, BM, BF, leptin, glucose, insulin and triglycerides. Summary information for each data subset is presented in Table 1. The number of data points (effect sizes) within each outcome ranged from 181 to 13 and the number of studies these data points were derived from ranged from 80 to 5. We obtained data on SBP and HDL-C only from few individual studies (Golubeva et al., 2015; Igosheva et al., 2007, 2004; Paternain et al., 2013) thereby meta-analyses were not performed. Table in SI 7 illustrates in the characteristics of the studies excluded from meta-analyses but included in systematic review (Golubeva et al., 2015). We refer the reader to the specific publications for details.

3.1.2. Effects of maternal stress on birth weight

Meta-analysis using a random-effects model indicated that MS resulted in a significant decrease in BW (d = -0.590, Table 2, Forest Plot in SI 8.1). To evaluate the robustness of our results against influential studies, a leaving-one-out sensitivity analysis was performed, which supported the stability of our analysis as no influential individual study could be identified (Table 2). High heterogeneity was detected among studies and for this reason subgroup analysis was conducted. Moderators modifying the effect of MS on BW were sex, intervention span, exposure period, stress model and maternal BM (SI 9.1). Meta-regression models were used to uncover the potential influence of the exposure duration and litter size. These analyses provide some evidence that the high heterogeneity could be explained by the length of maternal manipulation during gestation (Z-value = 3.4, SI 10.1).

3.1.3. Effects of maternal stress on body mass, body fat and leptin

MS proved to have a small but significant negative effect on offspring BM (d = -0.270, Table 2, SI 8.1). The leaving-one-out sensitivity analysis confirmed our results (Table 2). High heterogeneity was found and the test for subgroup differences showed that three moderators significantly modified the effect of MS (SI 9.1). Sex, stress model and exposure period showed significant between-study heterogeneity. Meta-analysis on Dataset 3 yielded similar results [d(95 %CI) = -0.597 (-1.049; -0.146), p-value = 0.01, n = 13].

Table 1
Summary of included data in meta-analyses of maternal stress.

Outcome	Birth Weight	Body Weight	Body Fat	Leptin	Glucose	Insulin	Triglycerides
N data points (N studies)	132 (75)	181 (80)	35 (13)	19 (8)	36 (15)	23 (10)	13 (5)
N data points male : female	46:27	103:55	20:14	12:7	20:12	14:8	8:5
N data points rat : mice	113:16	121:50	25:10	11:8	23:13	18:5	9:4
mean age (days)	NA	78.7	170.2	141.9	117.6	175.3	134.7

Notes: NA = not applicable.

Table 2
Meta- analyses of maternal stress: random-effects model, heterogeneity, publication bias (Egger's regression intercept) and one-study removed.

Outcome	Random effects model d ± 95 %CI	Heterogeneity		Egger's regression intercept ± SE	One-study removed d ± 95 %CI (range)
		Q-value	I-squared		
Birth Weight	−0.590 (-0.734; -0.447)***	1190***	89	−1.679 ± 0.460**	−0.609 (-0.751;-0.466) to −0.549 (-0.683;-0.415)
Body Mass	−0.270 (-0.392; -0.148)**	842***	79	−0.0703 ± 0.387	−0.283 (-0.404;-0.162) to −0.241 (-0.350;-0.133)
Body Fat	−0.300 (-0.516; -0.084) **	68 **	50	−0.843 ± 0.609	−0.347 (-0.544;-0.149) to −0.260 (-0.470;-0.050)
Leptin	−0.150 (-0.448; 0.147)	35 **	49	−4.194 ± 1.787 *	−0.213 (-0.500;0.073) to −0.089 (-0.375;0.197)
Glucose	0.011 (-0.215; 0.237)	103 ***	66	0.193 ± 0.590	−0.035 (-0.254;0.184) to 0.050 (-0.171;0.271)
Insulin	−0.120 (-0.530; 0.290)	65 ***	66	−0.880 ± 2.424	−0.251 (-0.582;0.080) to −0.018 (-0.393;0.358)
Triglycerides	0.211 (-0.233; 0.655)	28 **	57	1.114 ± 2.416	0.090 (-0.277;0.457) to 0.312 (-0.114;0.737)

Notes: d = standardized mean difference; SE = standard error.
* p-value <0.05.
** p-value <0.01.
*** p-value <0.00001.

An association between MS and BF was also detected (d=-0.300, Table 2, SI 8.1). BF in offspring of MS dams was significantly lower than in offspring of non-stressed dams. Decreases in leptin levels were not observed (Table 2, SI 9.1). The omit-one sensitivity analyses confirmed the results (Table 2). Low levels of heterogeneity were found in BF and leptin and mixed effects analyses were performed. In BF dataset no significant difference between study heterogeneity was detected; and in leptin dataset only moderator age stage could account for some heterogeneity. We used meta-regression models (SI 10.1) to uncover the potential influence of differences in experimental protocols, such as offspring age, exposure duration and weaning day, but we found that those moderators had no impact.

3.1.4. Effects of maternal stress on systolic blood pressure

We obtained the blood pressure data only from four separate publications. Table in SI 12.1 show data extracted from the studies excluded from the meta-analysis but included in the systematic review. In two different cohorts, exposure of pregnant rats to restraint and bright light during the last week of pregnancy did not lead to increases in SBP at rest in adult offspring (Holson et al., 1995.; Hougaard et al., 2005). However, in the same strain, other researchers described that animals subjected to restraint stress prenatally developed significant elevation of SBP in resting conditions (Gerardin et al., 2005). In rats, also cold stress during the last week of pregnancy was associated with an increase in SBP (Sun et al., 2019). Finally, one study conducted in C57BL/6 J mice reported a detrimental but sex-specific effect on SBP (Sreetharan et al., 2019).

3.1.5. Effects of Maternal Stress on glucose, insulin, triglycerides and HDL-Cholesterol

We found no general effect of MS on offspring glucose and insulin (Table 2, SI 8.1). Changes in glucose and insulin in MS offspring were not significantly different from those of non-stressed mothers. The stability of our analysis was confirmed by one-study removed analyses (Table 2). Moderate levels of heterogeneity were found in both glucose and insulin datasets (Table 2) and between-study heterogeneity was detected for some moderators (SI 9.1). Meta-regression models showed no significant effects of offspring age, exposure duration or weaning day (SI 10.1).

Meta-analysis of data on triglyceride levels was just exploratory (Table 2, SI 8.1). Random-effect model analysis showed no difference in blood triglycerides between offspring of MS and control dams. Moderate levels of heterogeneity were detected and leaving-one-out sensitivity analyses showed stability of our analysis (Table 2). Finally, we obtained HDL-C data from only one publication (SI 12.1). There was no detectable effect on serum HDL-C in adult offspring of dams exposed to unpredictable stress during gestation (Paternain et al., 2013).

3.1.6. Risk of bias

Sensitivity analyses were conducted to address the effect of studies at risk of bias and in general meta-analytic results were confirmed in Dataset 2 (SI 11.1).

3.1.7. Quality

The methodological quality scores ranged from 0 to 4 (SI 4.1). However, meta-regression models showed that quality score was not involved in the observed heterogeneity (SI 10.1), with one exception: quality score seemed to be implicated in the relationship between MS and BW (Z = 2.3). Other related moderators, such us year of publication, were further studied. Meta-regression models showed that year of publication was involved in heterogeneity in BW (Z = 2.3) and BF (Z = 2.5) datasets (SI 10.1). Publication bias was assessed through Egger's regression test and visually inspecting asymmetry in the funnel plots (data not shown). We found some evidence of publication bias in BW and leptin datasets (Table 2). However, such bias only persisted for BW dataset in Dataset 2 (SI 11.1).

3.2. Systematic review and meta-analyses on prenatal corticosteroid exposure

3.2.1. Characteristics of included studies

114 published studies were used in meta-analyses (References are available at SI 4.4). The characteristics of the selected studies are shown in SI 4.5 and data on timing of maternal manipulations are presented in SI 5.2. The studies included differed in the drugs used [mainly corticosterone, dexamethasone/ betamethasone and carbenoloxone (inhibitor of 11β-HSD2)] and in the doses and routes of administration (SI 6.2). The most commonly used drug was dexamethasone, a poor substrate for 11β-HSD2 that readily crosses the placenta.

We have performed seven separate meta-analyses on the relationship between PCE and outcomes under study: BW, BM, BF, leptin, SBP, glucose and insulin. Summary information for each data subset is presented in Table 3. The number of data points within each outcome ranged from 226 to 14 and the number of studies these data points were derived from ranged from 87 to 7. Since we obtained data on triglycerides and HDL-C from only a few publications, meta-analyses were not performed (Buhl et al., 2007; Cleasby et al., 2003a; Mark et al., 2014; Tsai et al., 2019). Table in SI 7 illustrates the characteristics of the studies excluded from meta-analyses but included in the systematic review (Mark et al., 2014).

Table 3
Summary of included data in meta-analyses of prenatal corticosteroid exposure.

Outcome	Birth Weight	Body Weight	Body Fat	Leptin	Glucose	Insulin	Systolic Blood Pressure
N data points (N studies)	156 (87)	226 (78)	14 (7)	27 (8)	30 (17)	26 (14)	56 (24)
N data points male : female	29:29	114:73	11:3	14:13	21:7	18:8	30:24
N data points rat : mice	131:18	194:24	14:0	27:0	27:3	26:0	52:3
mean age (days)	NA	67.7	105.9	97.3	134.3	148.8	135.9

Notes: not applicable.

3.2.2. Effects of prenatal corticosteroid exposure on birth weight

Meta-analysis of the 156 included data points revealed that PCE had a significant overall effect on neonatal weight [(d = -1.229), Table 4, SI 8.2]. The leaving-one-out sensitivity analysis supported the stability of our analysis (Table 4). High heterogeneity was detected and all studied moderators significantly modified the effect of PCE on BW (sex, species, administered drugs, exposure period and maternal BM) in mixed-effects analyses (SI 9.2). Meta-regression models (SI 10.2) also provided evidence that the high heterogeneity could be explained by litter size ($Z < 0$) and exposure duration ($Z < 0$).

3.2.3. Effects of prenatal corticosteroid exposure on body mass, body fat and leptin

PCE also programmed a reduction in offspring BM (d = -0.421, Table 4, SI 8.2) and the leaving-one-out sensitivity analysis confirmed the results (Table 4). Moderate heterogeneity was found in BM dataset. The test for subgroup differences showed that three moderators significantly modified the effect of PCE (SI 9.2): species, administered drugs, and exposure period. Meta-regression models also provided evidence that heterogeneity could be explained by exposure duration and weaning day (SI 10.2). Meta-analyses on Dataset 3 [d(95 %CI) = -0.630 (-0.794; -0.467), p-value < 0.0001, n = 43] yielded similar results.

Meta-analyses of data on BF and leptin levels were only exploratory (Table 4, SI 8.2). Random-effect model analyses showed a significant increase in BF (d = 0.610) and blood leptin (d = 0.549) in offspring of dams exposed to corticosteroids during gestation. The stability of our analysis was confirmed by one-study removed analysis (Table 4) and heterogeneity was detected in both datasets (Table 4).

3.2.4. Effects of prenatal corticosteroid exposure on systolic blood pressure

Meta-analysis showed increased SBP in offspring of dams exposed to PCE during gestation (d = 0.872, Table 4, SI 8.2]. The stability of our analysis was confirmed by one-study removed analysis (Table 4). High heterogeneity was detected when all studies were combined. Subgroup analysis detected significant subgroup heterogeneity in three variables: species, administered drugs, and exposure period (SI 9.2). Covariates offspring age, exposure duration and weaning day had no significant effect on effect size (SI 10.2).

3.2.5. Effects of prenatal corticosteroid exposure on glucose, insulin, triglycerides and HDL-cholesterol

There were no association between PCE and alterations in glucose metabolism (Table 4 and SI 8.2). The leaving-one-out study detected that excluding one study at a time changed the random-model pooled estimates qualitatively in insulin dataset, indicating that the results were not consistent (Table 4). Moderate levels of heterogeneity were found both in glucose and insulin datasets, but the studied moderators seemed not to be involved in between-study heterogeneity (SI 9.2). According to meta-regression models, offspring age, exposure duration and weaning day had no significant impact (SI 10.2).

We obtained data on lipids only from three separate publications (SI 12.2). Dexamethasone treatment during the last week of gestation did not modify triglycerides or HDL-C in adult offspring (Buhl et al., 2007; Cleasby et al., 2003a; Mark et al., 2014; Tsai et al., 2019; Welberg et al., 2001).

3.2.6. Risk of bias

Results of Dataset 2 meta-analyses were in the same direction as extended dataset (SI 11.2).

Table 4
Meta- analyses of prenatal corticosteroid exposure: random-effects model, heterogeneity, publication bias (Egger's regression intercept) and one-study removed.
Expand

Outcome	Random-effects model d ± 95 %CI	Heterogeneity		Egger's regression intercept ± SE	One-study removed d ± 95 %CI (range)
		Q-value	I-squared		
Birth Weight	−1.229 (-1.369; -1.090)***	1506***	90	−2.851 ± 0.380***	−1.246 (-1.390;-1.102) to −1.205 (-1.343;-1.067)
Body Mass	−0.421 (-0.516; -0.327)***	762***	70	−1.243 ± 0.276**	−0.431 (-0.524;-0.338) to −0.406 (-0.498;-0.314)
Body Fat	0.610 (0.175; 1.045)**	34*	62	−1.020 ± 3.504	0.490 (0.090;0.890) to 0.677 (0.229;1.125)
Leptin	0.549 (0.262; 0.836)**	42*	37	1.107 ± 1.304	0.484 (0.218;0.746) to 0.598 (0.326;0.870)
Systolic Blood Pressure	0.872 (0.623; 1.121)***	218***	75	1.950 ± 0.836*	0.820 (0.581;1.058) to 0.913 (0.674;1.152)
Glucose	0.164 (-0.079; 0.408)	56*	48	−2.238 ± 1.954	0.110 (-0.117;0.336) to 0.214 (-0.016;0.445)
Insulin	0.237 (-0.056; 0.530)	60**	58	0.304 ± 1.381	0.185 (-0.099;0.468) to 0.296 (0.023;0.570)

Notes: d = standardized mean difference; SE = standard error.
* p-value < 0.05.
** p-value < 0.01.
*** p-value < 0.00001.

3.2.7. Quality

The methodological quality scores ranged from 0 to 4 (SI 4.2). Quality score and year of publication seemed to be implicated in the effect of PCE on BW and BM (SI 10.2). Egger's regression test and funnel plots (data not shown) showed evidence of publication bias in BW, BM and SBP subsets (Table 4 and SI 11.2).

3.3. Effects of birth weight

We ran meta-regression analyses (not previously specified) to determine whether our meta-analytic results were influenced by BW effect size. The standardized difference in means for BW was entered into the model as moderator. Results are shown in SI 10 (scatterplots are also available). Interestingly, the association between MS and BM was not modulated by BW; however, the relationship between PCE and BM was significantly affected by BW with a positive slope ($Z > 0$).

4. Discussion

4.1. Main findings

In the present study, we analysed the consequences of MS on later life susceptibility to MetS intermediate phenotypes with varying results. Foetal development is a global public health concern, and poor foetal growth in particular has been proposed as a good indicator of perinatal and postnatal health.

Our systematic analysis performed on studies in laboratory rodents indicated that exposure to stressful conditions during development has adverse effects on offspring BW. Similar effects were found by PCE exposure highlighting the important role of corticosteroids in programming LBW. In line with our findings, a previous systematic review of antenatal corticosteroids in animal studies reported adverse effects on foetal growth (Aghajafari et al., 2002).

Biological characteristics, such as species, offspring sex, maternal BM and litter size were detected as possible sources of heterogeneity and therefore should particularly be taken into account according to the rationale of the study (SI 9 and 10). Maternal weight is considered to be a moderator variable of biological significance. Interestingly, a negative relationship between MS and maternal BM was found: maternal BM was decreased in 24 of 47 MS cohorts. Mixed effects analysis detected that moderator maternal BM can modify the effects of MS (or PCE) on BW. In this context it is difficult to isolate the effects of decreased maternal weight gain during gestation and MS (or PCE) per se. On the other hand, study design can certainly influence the conclusions of different studies. Moderators such as exposure period and the characteristics of the manipulation namely stress model or administered drugs, had some detectable influence on BW (SI 9). In addition, the extent of maternal effects on BW was modulated by exposure duration (SI 10).

It is now widely accepted that there is a strong association between foetal growth retardation / LBW and increased risk for hypertension, impaired glucose tolerance, obesity and Diabetes Mellitus type 2 later in life (Barker and Osmond, 1988; Levy-Marchal and Jaquet, 2004). An important question, however, is whether susceptibility to adult disease in LBW children is due to permanent adaptations to a suboptimal environment during foetal life, to subsequent accelerated infant growth, or to both of these factors (Jimenez-Chillaron and Patti, 2007). Humans and rodents with reduced BW may experience rapid postnatal compensatory catch-up growth. Thus, a role of postnatal growth trajectory as the important factor in the development of non-communicable diseases has been postulated (Barker et al., 1993; Barker and Osmond, 1986). The " rapid catch-up growth hypothesis" suggests that LBW per se does not increase the risk of non-communicable diseases, but accelerates postnatal growth. In this regard, a systematic review highlights the importance of rapid postnatal catch-up growth of LBW neonates (Kelishadi et al., 2015). Rapid postnatal catch-up growth can be therefore considered to be a modifiable risk factor for cardiovascular disease and associated phenotypes.

The finding of an inverse association between MS (or PCE) and offspring's BM was unexpected and clearly warrants further evaluation. Interestingly, offspring exposed to MS (or PCE) had decreased BW but failed to attain rapid catch-up growth. We performed a (not previously specified) meta-analysis in a LBW data subset obtained by including only cohorts with LBW (SI 13) and results supported the association between LBW and decreased BM. Further studies should clarify which aspects of this phenotype are programmed and which reflect homeostatic responses. Importantly, meta-regression models showed that the association between PCE and BM was at the same time modulated by the effect on BW ($Z > 0$, SI 10) indicating that PCE derived in decreased BW which contributed to decreased BM.

On the other hand, MS would persistently affect mother's behaviour and e.g. disturbances in maternal care during the lactating period would contribute to the long term effects on offspring (Maccari et al., 2003). To test this point we performed meta-analyses of Dataset 3 and showed that cross-fostering to non-stressed dams had the same effects on BM than staying with the same previously stressed mother (Sections 3.1.3 and 3.2.3). Besides, meta-regression demonstrated that weaning day had an effect on the relationship between PCE and BM ($Z > 0$) suggesting that a longer period of lactation correlates with a greater recovery in BM (SI 10.2).

According to meta-analyses, MS was associated with decreased BF with no changes in leptin levels. Entringer (Entringer et al., 2010) had reviewed the induction of stress during pregnancy in animal studies and found that the offspring were heavier and exhibited greater adiposity but particularly when exposed to a high-caloric diet. In rodents, prenatally stressed offspring exposed to a high-energy diet developed obesity, hyperinsulinemia and hyperglycemia, suggesting increased susceptibility to diet (Boersma et al., 2014; Paternain et al., 2012; Sheen et al., 2016; Tamashiro et al., 2009; Tsai et al., 2019). Thus evidence suggest that a stressful prenatal environment seems to prime for adverse metabolic conditions.

Excess glucocorticoid exposure in early pregnancy has demonstrated to programme higher blood pressure that persists in later life in different species such as sheep and humans (Dodic et al., 1998; Doyle et al., 2000). Here we found that PCE had a detrimental effect on basal SBP in rodents. Meta-regression indicated that BW can modify the association between PCE and SBP and the scatterplot shows that increasing negative effects on BW are correlated with increasing effects on SBP (SI 10.2). Overall, findings suggest that susceptibility to increased SBP in PCE rodents is mediated by LBW and is not related to rapid catch-up growth.

Exposure to MS or PCE was not associated with alterations in glycaemic control. Overall summary estimates were positive but not significant, although it is still possible that effects were too small to be reliable detected or that we collected insufficient data to detect the impact. Of note, exclusion of specific datasets turned pooled estimates for the association between PCE and insulinemia positive and significant (omit-one study, Table 4). More studies are required to shed light on this association. On the other hand, obstetric and neonatal outcomes should be carefully observed in future studies as we found that 1) the overall effect size for the relationship between MS and insulin was significantly influenced by BW ($Z > 0$, SI 10.2); and 2) maternal BM showed to be a significant moderator of the relationship between MS and circulating glucose and insulin (SI 9.1).

Evidence for an effect of MS on offspring's triglyceridemia was not conclusive because analysis was performed on a reduced number of datasets.

4.2. Strengths and limitations

As far as we know, this is the first study to systematically and quantitatively synthesize the available data on effects of MS on offspring's MetS-related phenotypes. A study of this sort can facilitate integration of the available knowledge, leading to more reliable conclusions and to a reduction of unnecessary duplication of animal studies. Meta-analyses on the effects of exogenous corticosteroid administration (or inhibition of 11β-HSD2) during pregnancy were also performed to characterize the direct phenotypic effects of corticosteroids. The main strength of this meta-analysis comes from the relatively high number of included studies and data points. However, this study has also some limitations. Nowadays, there is a broad and compelling use of the term stress however not all possible terms were included in our search. Nutritional and non-nutritional stresses during pregnancy due to factors such as hostile conditions (e.g. infection or hypoxia) or exposure to chemicals (e.g. pesticides), can lead to consequences for the foetus that are detrimental to health. The link between nutrient restriction, e.g. protein restriction, during pregnancy and offspring's health outcomes definitely merit discussion in a separate systemic review and meta-analysis. In fact, nutrition is a main player for foetal programming and we have previously demonstrated through meta-analysis the negative effects of maternal high-fat diet on foetal programming (Tellechea et al., 2017).

We observed significant low to high heterogeneity across all of our data which suggests that only under some specific conditions MS (or PCE) may influence offspring's phenotype. In each individual subgroup analysis there was a significant amount of unexplained heterogeneity and therefore none of the moderators could clearly account for the observed variation among studies (data not shown). Experimental designs varied widely among the included studies mainly because intervention is not yet standardized. Subgroup analysis gave insight into the relation between study characteristics and the effect size. First, in addition to differences in stress model (or drug, dose and intervention schedule), variability in the exposure period had appreciable influence, particularly on BW, BM and SBP. Secondly, another source of heterogeneity among studies reporting these outcomes emerged from the diversity of rodent species used. "Species" is a biological variable likely to contribute to heterogeneity. Accordingly, new meta-analyses were conducted to eliminate the between-study effects associated with variation among species. The rat dataset was processed and analyzed in the same manner as the extended dataset and results are presented in separate sections for MS and PCE in SI 14 and 15, respectively. In general meta-analytic results were confirmed in rat dataset with pooled estimates in the same direction as in extended dataset. Finally, gender is another important biological moderator shaping MS-related phenotypes, specifically BW, BM and insulin. Owing to differences in gender, the maternal intrauterine environment may be differently affected, and consequently the effect would be different (Dearden et al., 2018).

We found evidence for publication bias in BW (MS and PCE), BM (PCE), leptin (MS) and SBP (PCE) datasets that warrants further investigation of the factors influencing effect size. Publication bias might be particularly important when including studies with small sample sizes, because a few studies with neutral or negative results could materially affect the estimate; however this is not the case of BW and BM datasets. Given the levels of quantified heterogeneity within our datasets we believe that funnel plot asymmetry may be ascribed to between-study variation. Moreover, we did not take into account the methods of determination of the outcomes. Heterogeneity in SBP dataset probably owns to the different measurement methods used in the studies included, such as tail-cuff plethysmography, carotid cannulation and radiotelemetry.

The quality of the included studies was not always acceptable, with many papers showing incomplete reporting of relevant details. Moreover, quality score and year of publication proved to modulate results concerning BW, BM and BF. Finally, despite extensive searches, our findings are mainly based on rats and mice and our conclusions are for this reason not necessarily transferable to other laboratory rodents or mammals.

4.3. Translational potential

Development of relevant animal models is required to examine the aetiology of metabolic disorders. Since the mechanisms by which MS affects foetal and postnatal development remain poorly understood, we believe that this study will be an adequate starting point for future research in this area. This meta-analysis showed opposite effects of MS and PCE on adiposity (Tables 2 and 4) suggesting that foetal glucocorticoid exposure per se, and/or indirect effects of corticosteroid on maternal physiology, is not the single factor involved in MS physiopathology.

Studies concerning the effects of stressors on pregnant women had taken a special position in stress research. Littleton et al. (2010) meta-analysis evaluating the relationship between psychosocial stress in pregnancy and negative perinatal outcomes found that MS affects both neonatal weight and the risk for LBW (Littleton et al., 2010). MS during intrauterine life has also been shown to affect a range of long-term outcomes (Burgueño et al., 2019). A study has found evidence to suggest that exposure to stressful conditions during preconception and the prenatal period may increase the risk for developing Type 2 Diabetes Mellitus in childhood and young adulthood.

Glucocorticoids in pregnancy are prescribed for a number of conditions but mostly in the antenatal treatment of fetuses at risk of preterm birth or congenital adrenal hyperplasia (Kemp et al., 2015). Prenatal glucocorticoids administration to women at risk of preterm delivery was associated with higher blood pressure in their 14 year old offspring (Doyle et al., 2000). While treatment with synthetic glucocorticoids has been shown to increase the survival rate of preterm infants, major concerns have risen regarding the potentially short- and long-term harmful impact. Results of our meta-analysis in rodents contribute to evidence that glucocorticoids benefits in the short term need to be balanced against possible adverse health effects in later life. Besides SBP, researchers should also focus on BF, leptin and glucose metabolism (Table 4).

5. Conclusion

We found a link between MS during gestation and the adverse intrauterine environment predisposing the offspring to LBW. Importantly, MS was associated to LBW but not with rapid catch-up growth. It is possible that the observed effects on BM were due to unrecognized confounders or underestimates of the effects of known confounders. Future analyses in rodents should include data related to energy balance. We cannot conclude that there is an effect of MS on SBP, but programming of increased SBP in offspring that were exposed to corticosteroids in utero may occur. Despite the rationale for considering a role for stress in foetal programming of offspring health, we conclude that MS per se may give rise to subtle adverse effects in rodents, and abnormal phenotype may be provoked by or exacerbated in a later life challenging environment.

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Author contributions statement

MLT designed the study and performed data analysis/interpretation. MLT, ALB and YRJ screened titles/abstracts and performed data extraction. ALB and MLT determined eligibility of articles and assessed the quality of the included studies. ALB, AMG and MLT drafted the final manuscript. All authors contributed to the critical revision of the manuscript and approved the final version.

Data availability statement

Data of this study are available from PubMed except for unpublished data of our group which is available under request.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.104560.

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