Neuroscience and Biobehavioral Reviews 98 (2019) 107–121

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

The link between maternal obesity and offspring neurobehavior: A systematic review of animal experiments

Malou D. Menting[a,b,c,d,*], Cornelieke van de Beek[a,b,d], Stijn Mintjens[a,b,e], Kimberley E. Wever[f], Aniko Korosi[g], Susan E. Ozanne[h], Jacqueline Limpens[i], Tessa J. Roseboom[a,b,c,d], Carlijn Hooijmans[f,j], Rebecca C. Painter[a,b]

[a] Department of Obstetrics and Gynecology, Amsterdam UMC, location AMC, Amsterdam, the Netherlands
[b] Amsterdam Reproduction and Development Research Institute, Amsterdam UMC, Amsterdam, the Netherlands
[c] Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, location AMC, Amsterdam, the Netherlands
[d] Department of Pediatrics, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands
[e] Amsterdam Public Health Research Institute, Amsterdam UMC, Amsterdam, the Netherlands
[f] Department for Health Evidence unit SYRCLE, Radboud University Medical Center, Nijmegen, the Netherlands
[g] Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, the Netherlands
[h] Metabolic Research Laboratories and MRC Metabolic Disease Unit, University of Cambridge, Cambridge, United Kingdom
[i] Department of Research Support – Medical Library, Amsterdam UMC, location AMC, Amsterdam, the Netherlands
[j] Department of Anesthesiology, Radboud University Medical Center, Nijmegen, the Netherlands

ARTICLE INFO

Keywords:
Obesity
Pregnancy
Neurobehavior
Offspring
Animal experiments
Systematic review

ABSTRACT

Maternal obesity in pregnancy is associated with neurobehavioral problems in the offspring. Establishing causality has been challenging in existing human studies, due to confounding by genetic and postnatal environment. Animal experiments can improve our understanding of this association. This systematic review examined the effects of maternal obesity in pregnancy on offspring neurobehavior in animal models. We included 26 studies (1047 offspring animals). Meta-analyses showed that offspring of obese mothers displayed higher levels of locomotor activity (standardized mean difference (SMD) 0.34 [0.10; 0.58]) and anxiety behavior (SMD 0.47 [0.16; 0.79]) than offspring of lean mothers, but similar memory abilities (SMD −0.06 [−0.52; 0.39]). Meta-analysis of learning abilities was not sensible due to heterogeneity. Although the evidence was heterogeneous and the quality of the included studies generally unclear, this systematic review of animal studies indicates an effect of maternal obesity on increased offspring locomotor activity and anxiety, but not on offspring memory performance. These findings may be important from a public health perspective since obesity is rapidly increasing worldwide, and warrant further research.

1. Introduction

Worldwide, the prevalence of obesity (Body Mass Index (BMI) ≥ 30 kg/m^2) among women has risen dramatically over recent decades (Flegal et al., 2016; Ng et al., 2014). This rise has also been observed in pregnant women (Heslehurst et al., 2010; Poston et al., 2016). At present, approximately one third of women of reproductive age in the United States is obese (Flegal et al., 2016). Obesity before and during pregnancy (hereafter referred to as maternal obesity or obese mothers) is associated with pregnancy complications and adverse perinatal outcomes (Poston et al., 2016; Hanson and Gluckman, 2014).

Importantly, there is now accumulating evidence that maternal obesity has long term impact on the health of the offspring, including offspring neurobehavior (Hanson and Gluckman, 2014). Maternal obesity causes alterations in the prenatal environment of the growing fetus. For example, the developing brain is exposed to an increase of nutrients, inflammatory cytokines and to different levels of metabolic hormones (Rivera et al., 2015). This consequently may affect offspring neurobehavior later in life. Indeed, multiple observational studies have demonstrated that maternal obesity is associated with an increased risk of neurobehavioral problems in the offspring (Godfrey et al., 2017). For example, compared to children of mothers with normal weight, children of obese mothers had 40% higher odds of having emotional/behavioral problems and 60% higher odds of being diagnosed with a neurodevelopmental disorder, such as attention deficit-hyperactivity disorder (Sanchez et al., 2017). Moreover, children of obese mothers

* Corresponding author at: Amsterdam UMC Department of Obstetrics and Gynecology, Room H4-260, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands.
E-mail address: m.d.menting@amc.uva.nl (M.D. Menting).

https://doi.org/10.1016/j.neubiorev.2018.12.023
Received 13 July 2018; Received in revised form 19 December 2018; Accepted 19 December 2018
Available online 03 January 2019

show poorer cognitive performance than children born to mothers with a normal weight (Alvarez-Bueno et al., 2017; Adane et al., 2016): each unit increase in pre-pregnancy BMI is associated with a decrease in a half point of intelligence quotient (IQ) in the offspring at age 5 years (Bliddal et al., 2014). However, some but not all studies (Antoniou et al., 2014), that made use of sibling analyses (Chen et al., 2014) or analyses with paternal BMI (Gardner et al., 2015) have failed to find an association between maternal obesity and an increase in offspring neurobehavioral problems. Therefore, it is still unknown whether maternal obesity itself is causal to an increase in offspring neurobehavioral problems or that the observed link can be explained by other factors such as genetics (Chen et al., 2014) or parenting style (Van Lieshout, 2013).

Establishing whether maternal obesity directly causes offspring neurobehavioral problems has been challenging in existing human studies, since they are all observational and thereby subject to confounding. Experimental studies allow the investigation of the causal relation between maternal obesity and offspring neurobehavior. Experimental research in humans on this topic is difficult to perform and therefore experimental research in animals is needed. Also, relative to studies with humans, it is easier in animal experiments to follow the offspring for longer fractions of their lifespan to assess the long term neurobehavioral consequences of maternal obesity. Although numerous animal experiments have been performed on the causal effect of maternal obesity on neurobehavioral problems in the offspring (Rivera et al., 2015; Sullivan et al., 2014; Bolton and Bilbo, 2014; Edlow, 2017; Contu and Hawkes, 2017), the evidence has not yet been systematically reviewed or subjected to a meta-analysis. Therefore, the aim of the current study was to systematically review and quantitatively summarize the effect of maternal obesity on offspring's neurobehavior in previously published animal experiments.

2. Methods

The review protocol (first version at August, 28th 2015 and updated version at January 3th, 2017) was registered at the website of SYRCLE on January 11th, 2017 and can be accessed via the website: www.syrcle.nl. The reporting in this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

2.1. Search strategy

A medical information specialist (JL) performed a systematic search in OVID MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations) and OVID EMBASE from inception to January 30th, 2018 (initial search performed on June 24th, 2015, update search performed on January 30th, 2018). We searched for the following concepts, using both controlled terms (i.e. MESH) and text words: (i) animals; (ii) prenatal/maternal exposure (including maternal/intrauterine and offspring) and (iii) obese (including high-fat diet (HFD) and maternal/body weight/mass). Reviews, editorials and conference abstracts were excluded. No further restrictions were applied. We cross-checked the reference lists and the citing articles (via Web of Science) of relevant papers and review articles and adapted the search in case of additional relevant studies. The bibliographic records retrieved were imported and de-duplicated in ENDNOTE. The complete search strategies are presented in supplementary file 1.

2.2. Study selection

Two reviewers independently screened all identified articles for eligibility using Covidence (Covidence systematic review software, 2019), first by screening the title and abstract for eligibility of all identified publications (MM screened all; CvdB screened 70% and SM and CF screened each 15%) and secondly by screening the full manuscripts deemed potentially eligible after title and abstract screening (MM and SM). Disagreements were resolved by discussion or by consulting a third reviewer (RP).

2.3. Eligibility

Animal studies were eligible if they compared the neurobehavior of offspring born to females that were obese before and during pregnancy to offspring born to females that had a normal weight before and during pregnancy. We applied no limitation to animal species.

Obesity was defined as a statistically significant (as defined by the authors of the studies) higher body weight or a higher fat mass of experimental females compared to control females. For a study to be eligible, higher body weight and/or fat mass had to be present before pregnancy (defined as prior to mating or at mating), to ensure that offspring were exposed to maternal obesity during the entire gestational period. In case the weight/fat mass before pregnancy was not reported in the study article, but in the methods section of the study article it was reported that weight or fat mass was measured before pregnancy, the authors were contacted for weight/fat mass details. We assumed that obesity present before pregnancy continued to exist during pregnancy when the diet that had resulted in obesity continued, unless the article reported differently.

We excluded studies for the following reasons: (i) different postnatal environments between the experimental and control group; (ii) no normal/chow diet of offspring after weaning onwards (for example any obesogenic or low-calorie diet); (iii) an additional disease factor such as severe diabetes; (iv) interventions potentially interfering with the primary effect of maternal obesity (e.g., postnatal leptin injections); (v) lack of a control group with a normal weight and normal diet; (vi) different genetic background of experimental and control group; (vii) only data on molecular, epigenetic or fetal effects; (viii) reviews, editorials, conference abstracts and interviews.

2.4. Study characteristics and outcome data extraction

2.4.1. First phase

We extracted bibliographic details, animal species and strain, sex of the offspring, method of obesity induction, dietary information of the female animals and their offspring, maternal age at mating, type of outcome measure and age of the offspring at time of outcome assessment of the included studies. We (MM and CvdB) extracted data using a piloted data-extraction form. Of the studies of the initial search, 100% were extracted in duplo and of the studies in the update search, 20% were extracted in duplo. Due to negligible differences between the two assessors, no further data extraction of the update search in duplo was deemed necessary.

We divided the outcome measures into predefined categories as listed in our study protocol: physical activity (for example: spontaneous movements, exploratory behavior, motor activity), behavior (for example: stress, social behavior, emotional behavior, communication, avoidance, conditioning, anxiety) and executive functioning (for example: memory, attention, learning). Subsequently we selected up to two outcomes from each outcome category for further analysis. In order to be selected, the outcomes needed to be clinically important (as discussed within our author group) and reported in at least two independent articles included in our SR (of the initial search performed in June 2015). We selected the outcomes locomotor activity, anxiety, learning ability and memory.

2.4.2. Second phase

We extracted outcome data of the selected outcomes: means, standard deviations (SDs) or standard errors (SEs) and number of animals (N) with additional study variables (use of multiple or single litter(s), correction for litter size, paternal diet and cross-fostering). If results were only displayed graphically, the outcomes were read using a digital

screen ruler (Adobe Acrobat IX Pro). When SDs/SEMs overlapped within the figure and therefore it was not possible to extract the exact SD/SEM, we extracted the most conservative estimate and when this was not possible, we contacted the authors for data.

We extracted data using a piloted data-extraction form. A random selection of 15% of the data was extracted in duplo by a second reviewer (CvdB), blinded to the findings of reviewer one (MM) and any discrepancies were resolved by discussion. Due to negligible differences between the two assessors, data extraction of all data in duplo was not deemed necessary.

Some tests reported multiple outcomes (for example the Open Field test: 'time in center zone' and 'frequencies entering the center zone'). These outcomes were listed in order of relevance (through discussion of the authors MM, CvdB, CH, AK) resulting in a primary outcome (first outcome on the list) and alternative outcomes (all other outcomes on the list). An overview of the primary and alternative outcomes are shown in supplementary tables 1–3. For each study, the primary outcome was extracted. An alternative outcome was only extracted when the primary outcome was not available even after contacting the author.

2.5. Data analysis

2.5.1. Comparisons and subgroups

If a study reported separately on offspring outcomes of different maternal diets or offspring sex, we analyzed the groups as if they were separate studies.

When an outcome was measured more than once, measured using the same test and also in the same animal (for example when the Open Field tests was measured in the same animal at 6 and 8 weeks of age), the outcome values (mean and SDs/SEMs) were pooled. Since in some studies anxiety and memory were measured more than once using different tests in the same animal (for example Elevated Plus Maze and Open Field test were measured in the same animal), the test showing the largest difference between the offspring groups was used for the meta-analysis. With sensitivity analyses we assessed the robustness of this method by including all performed tests in the meta-analysis and dividing the N by the number of tests included in the analysis.

When a single control group served multiple experimental groups (for example when two types of high-fat diet were examined relative to the control group), the size of the control group was divided by the number of experimental-control comparisons. Therefore, one unique animal is only displayed once per outcome measure in the forest plot.

2.5.2. Meta-analyses

We performed the meta-analyses with STATA 15.0 (StataCorp, 2017). We calculated the standardized mean difference (SMD) for each separate experimental-control comparison group with Hedges' g correction (Hedges, 1985). In the meta-analysis, the individual SMDs were pooled to obtain an overall SMD and 95% confidence interval. A minimum of three studies *or* five independent comparisons was required for this meta-analysis. We used random effects models, which take into account the precision of individual studies and the variation between studies and weigh each study accordingly.

Subgroup analyses were pre-defined in the protocol and only performed when the subgroups contained a minimum of three studies *or* five independent comparisons. Subgroup analyses were performed according to sex (male, female, male + female in case the studies did not report on males and females separately), age (e.g. infants (birth - 3 weeks for mice and rats), juveniles (3–6 weeks for mice; 3–7 weeks for rats) and adults (6 weeks and older; 7 weeks and older for rats)) and species (rat, mouse, macaques) when possible.

We displayed the summary outcomes using 95% confidence intervals (CI) and calculated I^2 as a measure of heterogeneity. We considered P-values of less than .05 statistically significant. In order to test for subgroup differences we performed T-tests and adjusted our statistical significance level according to the conservative Bonferonni method to account for multiple analyses (P/number of comparisons). When the subgroups significantly differed from each other, we interpreted this as that subgroups explained some heterogeneity. Using post hoc analysis, we examined whether type of test used for the outcome measurement affected heterogeneity.

2.6. Quality assessment and risk of bias

The methodological quality of all selected studies was evaluated by the SYRCLE risk of bias tool for animal studies. The SYRCLE risk of bias tool is based on the Cochrane Risk of Bias tool and has been adjusted for aspects of bias that play a specific role in animal intervention studies (Hooijmans et al., 2014). A 'yes' score indicates low risk of bias; a 'no' score indicates high risk of bias; and a '?' score indicates unknown risk of bias.

Reporting of experimental details on animals, methods and materials is very poor (Avey et al., 2016). To overcome the problem of judging too many items as 'unclear risk of bias', we added three items on reporting: reporting of any measure of randomization, reporting of any measure of blinding, reporting of any measure of power size calculation. For these three items, a 'yes' score indicates 'reported', and a 'no' score indicates 'unreported'.

We displayed the answers to all questions separately and no aggregated quality was determined. Studies were not excluded based on a poor quality score.

2.7. Publication bias assessment

To assess publication bias, we assessed funnel plots of the SMD against $1/\sqrt{N}$ with the Duval and Tweedie Trim-and-Fill method (Duval and Tweedie, 2000; Zwetsloot et al., 2017). We assessed publication bias only for outcomes for which a minimum of 10 articles (i.e. locomotor activity, anxiety, learning ability and memory) had been included.

3. Results

3.1. Amendments to the study protocol

In advance, we had no indication of the amount of retrieved outcome measures on this topic. Because of limited resources, our first amendment (decided after the first phase of data extraction of the initial search) was to focus on the three of our outcome categories listed in the study protocol that were the most directly related to the topic neurobehavior. Therefore, we excluded the outcome categories 'brain structure' and 'food preference and eating behavior' that were listed in our study protocol. Second, one reviewer extracted all data and a random selection of studies was extracted in duplo, because of negligible differences between the two reviewers. Third, a post hoc analysis was performed to assess whether the type of test used in the study for outcome measurement explained heterogeneity.

3.2. Search results

The search yielded 2543 unique publications, of which 540 were considered eligible based on title and abstract screening (see Fig. 1). After reading the full text articles, 513 studies were excluded. The main reasons for exclusion were no/unknown obesity in the experimental group (N = 307) or no report on the selected neurobehavioral outcomes (N = 129). One additional study was not eligible because the experimental-control comparisons were reported in an unusable form (Wright et al., 2011). Ultimately, 26 studies (N = 1047 offspring animals) could be included in meta-analyses (Fig. 1).

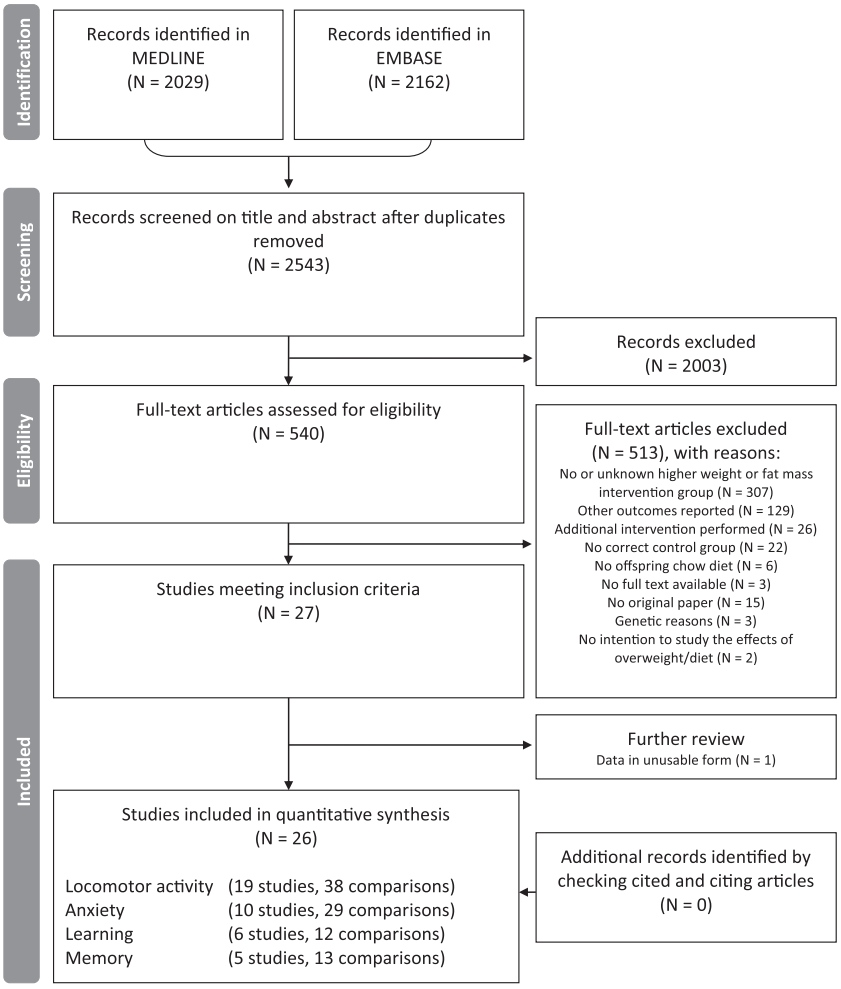

Fig. 1. PRISMA flow diagram.

3.3. Study characteristics

Table 1 provides an overview of the study characteristics and outcome measures. Included species were mice (N = 15 studies) (Balsevich et al., 2016; Bellisario et al., 2014; Chin et al., 2017; Dahlhoff et al., 2014; Fabian et al., 2015; Fernandes et al., 2012; Fernandez-Twinn et al., 2014; Graf et al., 2016; Kang et al., 2014; Mouralidarane et al., 2015; Samuelsson et al., 2008, 2013; Tozuka et al., 2010; Aburasayn et al., 2018; Buffington et al., 2016), rats (N = 10 studies) (Bahari et al., 2013; Bilbo and Tsang, 2010; Caruso et al., 2013; Robb et al., 2017; Ruegsegger et al., 2017; Sasaki et al., 2014, 2013; Shalev et al., 2010; White et al., 2009; Wu et al., 2013) and macaques (N = 1 study) (Thompson et al., 2017). Maternal obesity was induced by diet in the majority of the studies (N = 25) or by a combination of diet and litter size reduction in early life (N = 1) (Fabian et al., 2015).

3.4. Study quality

Table 3 shows the risk of bias assessment of the included studies. Six studies reported on randomization, three on blinding and no study on power or sample size calculation. Following the results of the SYRCLE Risk of Bias tool, all studies had an overall unclear risk of bias (Table 3). There was insufficient contrast between studies to perform sensitivity analyses according to study quality.

3.5. Locomotor activity

Nineteen studies with 38 separate experimental-control comparisons (hereafter referred to as comparisons) measured locomotor activity in the offspring. Locomotor activity was measured in a (metabolic) cage in nine studies (sixteen comparisons) (Dahlhoff et al., 2014; Fernandez-Twinn et al., 2014; Mouralidarane et al., 2015; Samuelsson et al., 2013; Aburasayn et al., 2018; Ruegsegger et al., 2017; Shalev et al., 2010; Wu et al., 2013); with an open field test in seven studies (fourteen comparisons) (Balsevich et al., 2016; Bellisario et al., 2014; Fabian et al., 2015; Fernandes et al., 2012; Kang et al., 2014; Tozuka et al., 2010; Buffington et al., 2016); a running wheel in four studies (twelve comparisons) (Chin et al., 2017; Bahari et al., 2013; Caruso et al., 2013; Ruegsegger et al., 2017) and an accelerometer in one study (two comparisons) (Thompson et al., 2017). Maternal obesity led to an increase in offspring locomotor activity (Fig. 2, SMD .34 [.10; .58], $p < .01$). Subgroup analysis showed that the effects of maternal obesity on offspring locomotor activity were not different for offspring sex and species, but the effect was different for juvenile and adult offspring: the increased locomotor activity was observed in juvenile offspring (N = 343) of obese mothers and not in adult offspring (N = 496) of obese mothers (supplementary Fig. 1–3).

The heterogeneity (I^2) of the overall analysis was 70.9%. Except for offspring age, the other predefined subgroups based on the variables sex and species did not explain the heterogeneity. A post hoc analysis into the effect of the type of test used to measure offspring locomotor activity also did not lower heterogeneity (cage/accelerometer activity: SMD .57 [.30; .84] with $I^2 = 40.4\%$, open field test: SMD .29 [-.06; .65] with $I^2 = 58.3\%$ and running wheel: SMD .17 [-.38; .73] with $I^2 = 81.0\%$).

Table 1
Study characteristics of the included studies.

Reference	Species, strain	Outcome measure	N	Sex offspring	Age offspring measurement	Maximum of separate experimental-control comparison within one outcome	Notes
Aburasayn et al. (2018)	Mice, C57BL/6 J	• Locomotor activity, Cage activity	3	F	8 weeks	1	Males were not measured in the study because there was no body weight difference between the experimental and control group before 8 weeks.
Bahari et al. (2013)	Rats, Sprague-Dawley	• Locomotor activity, Running wheel	24	F	10-15 weeks	1	Average over 10-15 weeks old was extracted.
Balsevich et al. (2016)	Mice, C57BL/6 J	• Locomotor activity, OF • Anxiety, EPM	44	M	3 months 12 months (Different animals used)	2	
Bellisario et al. (2014)	Mice, KO-p66ˆShc-/- and WT-66ˆShc+/+; C57Bl6/J background	• Locomotor activity, OF	12	M + F	12.5 weeks	1 (mice with different genetic background were grouped together)	Anxiety: OF and EPM were performed but no primary or alternative outcome measures were reported.
Bilbo and Tsang, (2010)	Rats, Sprague-Dawley	• Anxiety, EPM • Memory, MWM • Learning, MWM	48	M + F	3-4 months	4 (SFD and TFD diet, M and F offspring)	
Buffington et al. (2016)	Mice, C57BL/6 J	• Locomotor activity, OF • Anxiety, OF	44	M	7-12 weeks	1	
Caruso et al. (2013)	Rats, Sprague-Dawley	• Locomotor activity, Running wheel	28	M	4-10 weeks	1	Average over 4-10 weeks old was extracted.
Chin et al. (2017)	Mice, C57BL/6 J	• Locomotor activity, Running wheel	143	M + F	16-19 weeks	2	Two cohorts were used. Additionally, a subset of animals of the second cohort had locomotor activity measurement, but only the measurement of the whole group was extracted.
Dahlhoff et al. (2014)	Mice, NMRI	• Locomotor activity, Cage activity	28	M + F	5 months	2 (M and F offspring)	
Fabian et al. (2015)	Mice, ICR (CD-1 IGS) strain	• Locomotor activity, OF • Anxiety, OF	120	M + F	32-36 days	1	
Fernandes et al. (2012)	Mice, C57BL/6 J	• Locomotor activity, OF • Anxiety, OF and LD	17	M	4-5 months	2 (two tests anxiety)	Authors provided additional information on total distance travelled and time spent in center zone (OF).
Fernandez-Twinn et al. (2014)	Mice, C57BL/6 J	• Locomotor activity, Cage activity	11	M	8 weeks	1	
Graf et al. (2016)	Mice, C57BL/6 J	• Memory, Y-maze and novel object recognition	25	M + F	12 weeks	4 (M and F offspring, two tests memory)	Data was displayed in boxplots. Authors provided additional information on the mean and standard error.
Kang et al. (2014)	Mice, C57BL/6 J	• Locomotor activity, OF • Anxiety, OF	109	M + F	32-35 days	4 (HFD and CD lactation diet, M and F offspring)	Alternative outcome was extracted for anxiety, OF.
Mouralidarane et al. (2015)	Mice, C57BL/6 J	• Locomotor activity, Cage activity	6	F	6 months	1	Locomotor activity during light period. Locomotor activity during dark period was measured but not reported and was also not available when contacting author.
Robb et al. (2017)	Rats, Sprague-Dawley	• Learning, MWM • Memory, MWM	32	M + F	40-48 days	2 (M and F offspring)	At 90-98 days the MWM was also performed in the same animals. The animals remembered the task. Therefore the measurements at 90-98 days were not extracted.
Ruegsegger et al. (2017)	Rats, Wistar	• Locomotor activity, Wheel Running and Cage activity	32	M + F	Running wheel: 4-7 weeks 16-19 weeks Cage activity: 6 weeks 18 weeks	8 (M and F offspring; two tests; two age groups per test)	Two generations were reported in the study article, first generation was used for analyses.
Samuelsson et al. (2008)	Mice, C57BL/6 J	• Locomotor activity, Cage activity	24	M + F	3 and 6 months	2 (M and F offspring)	
Samuelsson et al. (2013)	Mice, C57BL/6 J	• Locomotor activity, Cage activity	28	M + F	3 months	2 (M and F offspring)	
Sasaki et al. (2013)	Rats, Long Evan	• Anxiety, OF, EPM and LD	51	M + F	Adulthood	6 (M and F offspring, three tests anxiety)	Alternative outcome was extracted for anxiety, EPM and LD.

(*continued on next page*)

Table 1 (*continued*)

Reference	Species, strain	Outcome measure	N	Sex offspring	Age offspring measurement	Maximum of separate experimental-control comparison within one outcome	Notes
Sasaki et al. (2014)	Rats, Long Evan	• Anxiety, OF, EPM and LD	70	M + F	35-45 days	6 (M and F offspring, three tests anxiety)	Alternative outcome was extracted for OF and EPM.
Shalev et al. (2010)	Rats, Wistar	• Locomotor activity, Cage activity • Learning, Sucrose-taking behavior (operant conditioning)	17	M	60-70 days	1	
Thompson et al. (2017)	Macaques, Japanese Macaques	• Locomotor activity, Accelerometer • Anxiety, Novel object	45	M + F	11 months	Physical activity: 2 (M and F offspring) Anxiety: 1 (M and F offspring combined)	Physical activity was also measured after the anxiety tests, but this was not extracted (physical activity after a stressful event). Anxiety was also measured with the human intruder test but this was not extracted (social anxiety).
Tozuka et al. (2010)	Mice, C57BL/6 J	• Locomotor activity, OF • Anxiety, OF • Learning, BM • Memory, BM	38	M	3-4 weeks 10-11 weeks (Different animals used)	2 (Different age groups)	
White et al. (2009)	Rats, Long Evan	• Learning, MWM • Memory, MWM	18	M	29 weeks	1	
Wright et al. (2011)	Rats, Wistar	• Locomotor activity, OF • Anxiety, OF and EPM	?	M + F	10 weeks	?	Data was presented in unusable form.
Wu et al. (2013)	Rats, Wistar	• Locomotor activity, Cage activity • Learning, VDSRL and ASST	30	M	Unknown	4 (HFD and HPD diet, two tests learning)	

Note. OF = Open Field test, EPM = Elevated Plus Maze test, LD = light Dark box/transition, MWM = Morris Water Maze, BM = Barnes Maze, VDSRL = Visual Discrimination and Serial Learning, ASST = Attentional Set Shifting Task, NR = Novel object Recognition, YM = Y-maze, M = Male, F = Female, SFD = high Saturated-Fat Diet, TFD = high Trans-Fat Diet, MFD = Moderate Fat Diet, HFD = High-Fat Diet, CD = Control/normal/chow Diet, HPD = Highly Palatable Diet.

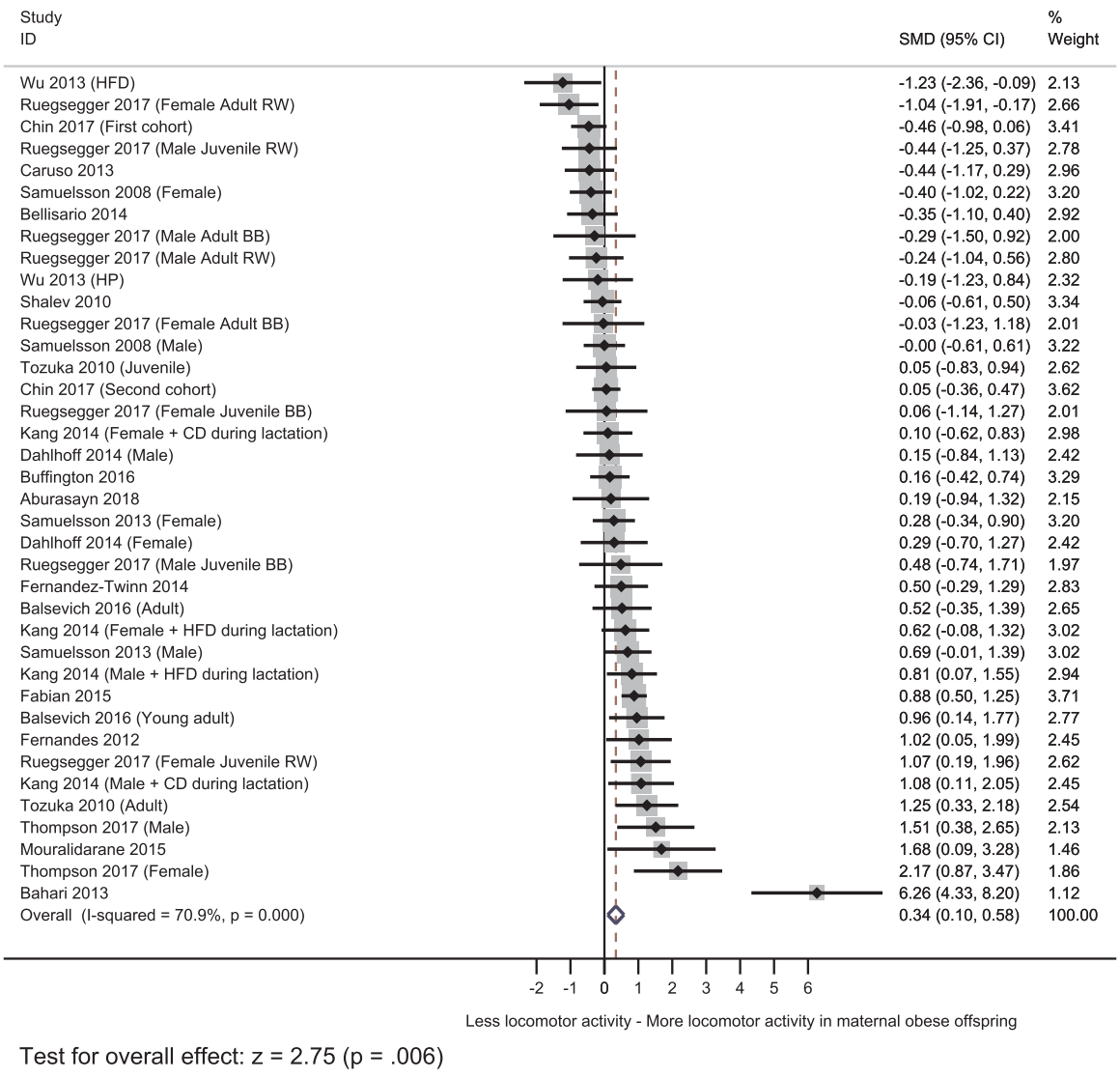

Fig. 2. Forest plot (effect size and 95% CI) of individual comparisons of offspring of obese mothers versus offspring of non-obese mothers on locomotor activity. *Note.* HFD = High-Fat Diet, BB = Beam breaks, RW = Running Wheel, HP = Highly Palatable diet, CD = Control/normal/chow Diet.

3.6. Anxiety

Ten studies (Balsevich et al., 2016; Fabian et al., 2015; Fernandes et al., 2012; Kang et al., 2014; Tozuka et al., 2010; Buffington et al., 2016; Bilbo and Tsang, 2010; Sasaki et al., 2014, 2013; Thompson et al., 2017) with twenty-nine comparisons measured offspring anxiety. In case anxiety was measured with multiple tests in the same animals (Fernandes et al., 2012; Sasaki et al., 2014, 2013), the test with the largest effect was included in our meta analyses. As a consequence, anxiety was measured with the Elevated Plus Maze test in three studies (seven comparisons) (Balsevich et al., 2016; Bilbo and Tsang, 2010; Sasaki et al., 2013), the Open Field test in five studies (ten comparisons) (Fabian et al., 2015; Kang et al., 2014; Tozuka et al., 2010; Buffington et al., 2016; Sasaki et al., 2014), the Light-Dark box in two studies (two comparisons) (Fernandes et al., 2012; Sasaki et al., 2013) and with the Novel Object test in one study (one comparison) (Thompson et al., 2017). Overall pooled analyses showed significantly higher anxiety levels in offspring of obese mothers relative to offspring of non-obese mothers (Fig. 3, SMD .47 [.16; .79], $p = .004$). Subgroup analysis showed that the effects of maternal obesity on offspring anxiety were not different for offspring sex, age and species (Supplementary figure 4–6). Sensitivity analysis (see method Section 2.5 *comparisons and subgroups*) did not lead to different results: it showed an effect of maternal obesity on increased offspring anxiety (SMD 0.28 [0.03; 0.53]).

The heterogeneity (I^2) of the overall analysis was 70.3%. Subgroup analyses showed that offspring sex, age and species did not lower the heterogeneity. Also, a post hoc analysis into the type of test used to measure anxiety did not explain heterogeneity (Elevated Plus Maze test: SMD 0.39 [−0.52; 1.30] with $I^2 = 83.0\%$ and Open Field test: SMD 0.48 [0.15; 0.80] with $I^2 = 60{,}8\%$).

3.7. Learning ability

Six studies (Tozuka et al., 2010; Bilbo and Tsang, 2010; Robb et al., 2017; Shalev et al., 2010; White et al., 2009; Wu et al., 2013) with twelve comparisons described the effect of maternal obesity on learning abilities. The visuo-spatial learning abilities in a non-food related context were assessed with the Morris Water Maze in three studies (seven comparisons) (Bilbo and Tsang, 2010; Robb et al., 2017; White et al., 2009) and the Barnes Maze in one study (two comparisons) (Tozuka et al., 2010). The simple and reversal learning abilities of the offspring in a food-related context were assessed with the sucrose-taking behavior test in one study (one comparison) (Shalev et al., 2010), the Visual Discrimination and Serial Reversal Learning task in one study (two comparisons) (Wu et al., 2013) and the Attentional Set-Shifting task in

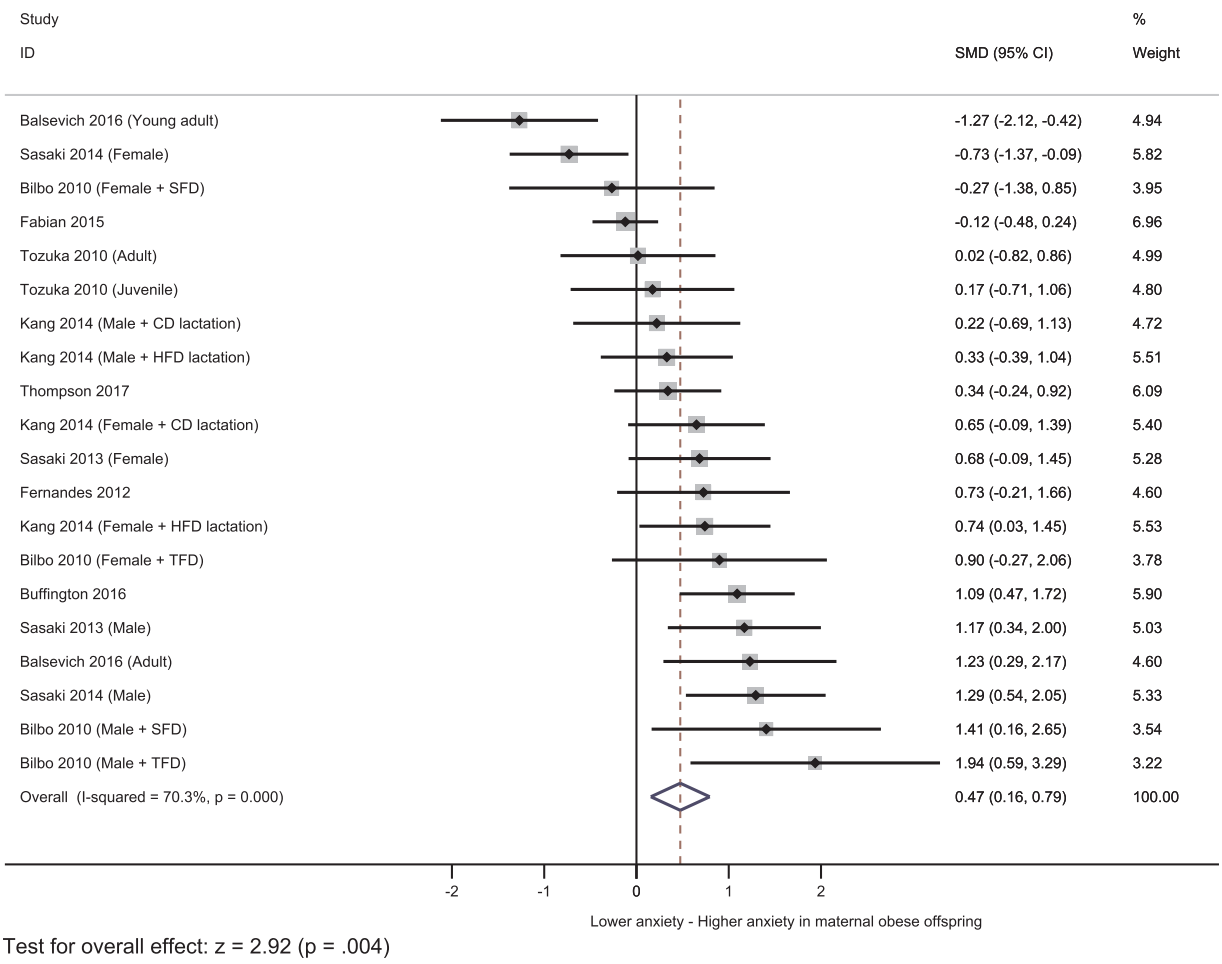

Fig. 3. Forest plot (effect size and 95% CI) of individual comparisons of offspring of obese mothers versus offspring of non-obese mothers on anxiety. *Note.* EPM = Elevated Plus Maze test, OF = Open Field test, SFD = high Saturated-Fat Diet, LDT = light Dark Transition, CD = Control/normal/chow Diet, LDB = Light/Dark Box, TFD = high Trans-Fat Diet.

one study (two comparisons) (Wu et al., 2013). Studies were too heterogeneous in type of test and outcomes used (Table 2) and therefore meta-analysis was not sensible.

Table 2 qualitatively summarizes the findings of the studies per comparison. Analysis of the results by using vote counting did not suggest differences in learning abilities between offspring of obese mothers versus offspring of normal weight mothers. Four comparisons out of four studies (Tozuka et al., 2010; Robb et al., 2017; Shalev et al., 2010; White et al., 2009) showed no differences in learning abilities of offspring of obese mothers versus offspring of non-obese mothers based on the authors conclusions. Four comparisons out of three studies (Tozuka et al., 2010; Robb et al., 2017; Wu et al., 2013) showed impaired learning ability and four comparisons out of one study (Bilbo and Tsang, 2010) showed improved learning ability of offspring of obese mothers versus non-obese mothers.

3.8. Memory

Five studies with thirteen comparisons (Graf et al., 2016; Tozuka et al., 2010; Bilbo and Tsang, 2010; Robb et al., 2017; White et al., 2009) assessed the memory of the offspring. In case memory was measured with multiple tests in the same animals (Graf et al., 2016), the largest effect was included in our meta analyses. As a consequence, memory was assessed with the Morris Water Maze in three studies (seven comparisons) (Bilbo and Tsang, 2010; Robb et al., 2017; White et al., 2009); with the Barnes Maze test in one study (two comparisons) (Tozuka et al., 2010); with the Y-maze in one study (one comparison) (Graf et al., 2016) and with the Novel Object Recognition test in one study (one comparison) (Graf et al., 2016). Overall analysis showed that offspring of obese mothers did not differ in memory from offspring of non-obese mothers (Fig. 4, SMD −0.06 [−0.52; 0.39], $p = 0.79$). Subgroup analysis showed that the effect of maternal obesity on offspring memory was not different for offspring sex (Supplementary figure 7). Subgroup analysis for age and species was not possible due to insufficient number of studies and numbers of comparisons. Sensitivity analysis (see method Section 2.5 *comparisons and subgroups*) did not lead to a different result: it showed no effect of maternal obesity on offspring memory (SMD −0.06 [-0.45; 0.33]). (Fig. 5)

The heterogeneity (I^2) in the overall analysis was 53.0%. Subgroup analysis for offspring sex did not lower the heterogeneity. Due to insufficient number of studies and comparisons, we could not assess with a post hoc analysis whether type of test was responsible for heterogeneity.

3.9. Publication bias

Inspection of the funnel plot for locomotor activity did not show asymmetry (Fig. 5A). Inspection of the funnel plot for anxiety suggested asymmetry due to an underrepresentation of studies with moderate precision and decreased anxiety in the offspring as a consequence of maternal obesity. Duval and Tweedie's Trim and Fill analysis resulted in three extra data points (Fig. 5B), indicating the presence of publication bias and a small overestimation of the summary effect size. The adjusted estimated effect size was SMD .35 [.03; .66], whereas the

Table 2
The effect of maternal obesity on offspring learning abilities.

Study reference	Test, learning domain	Unit of measurement	Amount of trials and days	Trial data that are reported in the study article	Separate experimental-control comparison within one outcome	Outcome
Bilbo and Tsang, (2010)	Morris Water Maze, Visuo-spatial learning	Latency to platform	10 trials per day for 2 days	All separate trials	Male SFD	↑
					Female SFD	↑
					Male TFD	↑
					Female TFD	↑
Robb et al. (2017)	Morris Water Maze Visuo-spatial learning	Latency to platform, distance travelled	4 trials per day for 3 days	Trials per day averaged and trials over three days averaged	Male	↓
					Female	↔
Shalev et al. (2010)	Sucrose-taking behavior, Food-related conditioning	Sucrose infusions/60 min, active lever responses/60 min	8 days several fixed ratio-1 trials, 10 days several progressive ratio trials	Trials per day averaged	N/A*	↔
Tozuka et al. (2010)	Barnes Maze, Visuo-spatial learning	Distance covered to reach the target hole	3 trials per day for 6 days	Trials per day averaged	Male Juvenile	↓
					Male Adult	↔
White et al. (2009)	Morris Water Maze, Visuo-spatial learning	Latency to platform, distance travelled	4 trials per day for 3 days	All separate trials	N/A*	↔
Wu et al. (2013)	Visual Discrimination and Serial Reversal Learning & Attentional Set-shifting task, Food-related learning and reversal learning	Main measures: number of trials to criterion, number of errors to criterion, type of error, latency to collect the reward, probability of shifting after an error or a correct response	Several trials per day, different learning phases.	Trials per learning phase averaged	HFD	↓ ↔
					HPD	↓ ↔

Faster learning for offspring of obese mothers ↑.
No difference between the offspring groups↔.
Slower learning for offspring of obese mothers↓.
Impaired reversal learning, but no difference in basal learning ↓↔.
* Only one separate experimental-control comparison in the study (see Table 1). SFD = high Saturated-Fat Diet, TFD = high Trans-fat Diet, HFD = High-Fat Diet, HPD = Highly Palatable Diet, N/A = Not Applicable.

Table 3
Risk of bias assessment.

Study reference	Reporting questions			Risk of bias questions										
	Randomi-zation	Blinding	Power/ sample size calculation	Was the allocation sequence adequately generated and applied?	Were the maternal groups similar at baseline or adjusted for confounders? *Species, strain, age and weight*	Were the offspring groups similar at baseline or adjusted for confounders? *Species, strain, age, sex and litter size*	Was the allocation adequately concealed?	Are the animals adequately randomly housed during the experiment?	Were the caregivers/ investigators during the course of the exp. adequately blinded?	Were animals selected at random (adequately) during outcome assessment?	Was the outcome assessment adequately blinded?	Were incomplete outcome data adequately addressed?	Are reports of the study free of selective outcome reporting? *Study protocol, all outcomes described in method are reported in results*	Was the study apparently free of other problems that could cause a high risk of bias? *Conflict of interest statement*
Aburasayn et al. (2018)	N	N	N	?	Y	Y	?	?	?	?	?	N	?	Y
Bahari et al. (2013)	N	N	N	?	Y	Y	?	?	?	?	?	?	?	Y
Balsevich et al. (2016)	N	N	N	?	?	?	?	?	?	?	?	?	?	Y
Bellisario et al. (2014)	Y	N	N	?	?	N	?	?	?	?	?	?	?	Y
Bilbo and Tsang, (2010)	N	N	N	?	Y	Y	?	?	?	?	?	?	?	?
Buffington et al. (2016)	N	N	N	?	?	N	?	?	?	?	?	?	?	?
Caruso et al. (2013)	N	N	N	?	?	Y	?	?	?	?	?	?	?	?
Chin et al. (2017)	N	N	N	?	Y	N	?	?	?	?	?	N	?	Y
Dahlhoff et al. (2014)	Y	N	N	?	Y	Y	?	?	?	?	?	?	?	?
Fabian et al. (2015)	Y	N	N	?	Y	Y	?	?	?	?	?	?	?	?
Fernandes et al. (2012)	N	Y	N	?	?	Y	?	?	?	?	?	?	N	Y
Fernandez-Twinn et al. (2014)	N	N	N	?	?	Y	?	?	?	?	?	?	?	Y
Graf et al. (2016)	Y	Y	N	?	Y	?	?	?	?	?	Y	?	?	Y
Kang et al. (2014)	N	N	N	?	Y	Y	?	?	?	?	?	?	?	Y
Mouralidarane et al. (2015)	N	N	N	?	?	Y	?	?	?	?	?	?	N	Y
Robb et al. (2017)	Y	N	N	?	Y	Y	?	?	?	?	?	?	?	?
Ruegsegger et al. (2017)	N	N	N	?	?	Y	?	?	?	?	?	?	?	Y
Samuelsson et al. (2008)	N	N	N	?	N	?	?	?	?	?	?	?	?	?
Samuelsson et al. (2013)	N	N	N	?	?	Y	?	?	?	?	?	?	?	Y

(*continued on next page*)

Table 3 (*continued*)

Study reference	Reporting questions			Risk of bias questions																	
Sasaki et al. (2013)	N	N	N	?		?		Y		?		?		?		?		?		?	
Sasaki et al. (2014)	N	N	N	?		?		Y		?		?		?		?		?		?	
Shalev et al. (2010)	Y	N	N	?		?		Y		?		?		?		?		?		?	
Thompson et al. (2017)	N	Y	N	?		?		?		?		?		?		?		?		?	Y
Tozuka et al. (2010)	N	N	N	?		Y		Y		?		?		?		?		?		?	
White et al. (2009)	N	N	N	?		Y		Y		?		?		?		?		?		?	
Wu et al. (2013)	N	N	N	?		Y		?		?		?		?		?		?		?	Y

Note. Reporting questions: a 'yes' score indicates 'reported', and a 'no' score indicates 'unreported'. Risk of bias questions: 'yes' indicates low risk of bias; a 'no' score indicates high risk of bias; and a '?' score indicates unknown risk of bias.

unadjusted SMD was: .52 [.20; .84] (note: this SMD was slightly different from the overall analyses displayed in Fig. 3 since the Trim and Fill analyses is based on a different precision estimate, e.g. $1/\sqrt{N}$ instead of SE). The number of studies on the outcome memory was too small to assess publication bias.

4. Discussion

Although the evidence was heterogeneous and the quality of the included studies generally unclear, this systematic review of animal studies indicates that maternal obesity before and during pregnancy is linked to an increase in offspring locomotor activity and anxiety behavior but does not affect offspring memory. The studies measuring offspring learning ability were too heterogeneous for meta-analysis. The effects of maternal obesity on offspring neurobehavior were present regardless of offspring sex, age or species, except for offspring locomotor activity: juvenile but not adult offspring of obese mothers displayed increased locomotor activity when compared to offspring of normal weight mothers.

4.1. Potential mechanisms

Although the exact mechanism by which maternal obesity is related to offspring neurobehavior remains unknown, several potential mechanisms have been proposed (Rivera et al., 2015; Sullivan et al., 2014). For example, offspring of obese mothers are exposed to an excess of nutrients (fatty acids, glucose), an excess of metabolic hormones (leptin) and higher levels of inflammatory cytokines in utero than offspring of mothers with a normal weight (Rivera et al., 2015). These factors have immediate effects on the offspring's developing neuroendocrine system, neural pathways and brain structure (Rivera et al., 2015) in utero as well as later in life through programmed epigenetic mechanisms (Contu and Hawkes, 2017; Moody et al., 2017). This change in neuroendocrine systems, neural pathways and brain structures in turn increases the chance of neurobehavioral alterations in the offspring (Rivera et al., 2015; Sullivan et al., 2015).

All of the animal models included in this systematic review, induced maternal obesity with an obesogenic diet. Another causal pathway that also has been demonstrated in rodent models could be that maternal high fat diet alters maternal behavior: an increase in nursing and a decrease in maternal grooming behavior was observed among HFD fed mother-offspring pairs when compared to normal fed mother-offspring pairs. This maternal behavioral change leads to increased anxiety-like behavior in her offspring, possibly mediated by altered offspring hypothalamic pituitary adrenal (HPA) regulation, or permanent epigenetic modification of endocrine systems in the offspring (Sullivan et al., 2015).

4.2. Clinical implications

The association of maternal obesity with increased activity and anxiety in the offspring could be important for public health since the rate of maternal obesity is increasing worldwide (Ng et al., 2014). At present, some animal studies have shown that dietary (Rodriguez et al., 2012; Zambrano et al., 2010) and exercise interventions (Vega et al., 2015; Moser et al., 2017; Fernandez-Twinn et al., 2017) before and during pregnancy may have beneficial effects on the offspring. Importantly however, the translation from our results to humans is not straightforward.

Our meta-analyses showed an effect of maternal obesity on increased locomotor activity, which was independent of the type of test used. This suggests that locomotor activity in the offspring is increased regardless of the setting: voluntary locomotor activity (for example wheel running), spontaneous locomotor activity in the cage and activity in an anxiety provoking environment (Garland et al., 2011). However, translating the concept of rodent's locomotor activity to humans is

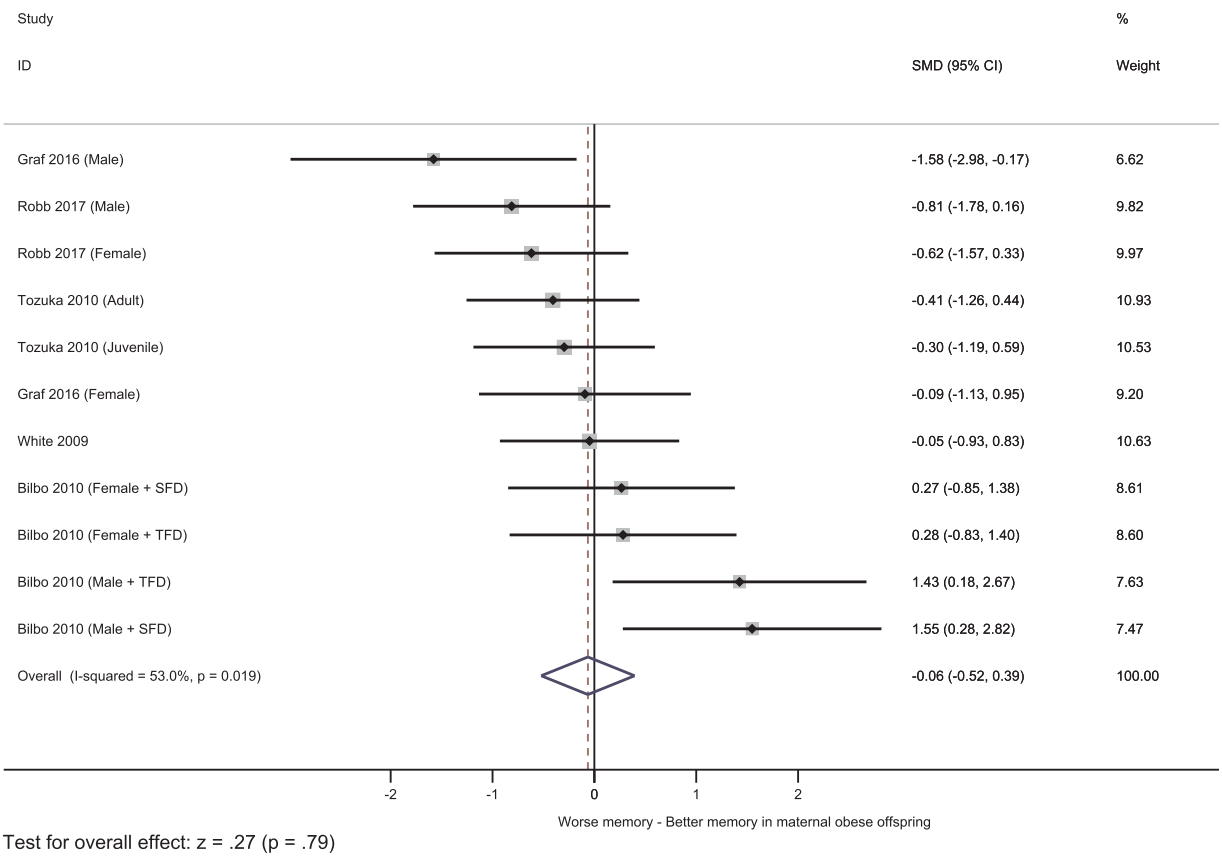

Fig. 4. Forest plot of individual comparisons of offspring of obese mothers versus offspring of non-obese mothers on memory. *Note.* NR = Novel object Recognition, YM = Y-Maze, SFD = high Saturated-Fat Diet, TFD = high Trans-Fat Diet.

challenging (Garland et al., 2011). Offspring increased locomotor activity in animals has been frequently interpreted as increased hyperactivity (Rivera et al., 2015; Fernandes et al., 2012; Kang et al., 2014). Our results would thereby support findings of human observational studies showing that maternal obesity is associated with an increase in children's hyperactivity (Sanchez et al., 2017). Alternatively, increased locomotor activity could be interpreted as an increased (innate) motivation to exercise or as a decrease of sedentary behavior (Garland et al., 2011). If this would apply here, increased activity could be beneficial for the offspring, since increased activity is linked to improved physical and mental health (Landry and Driscoll, 2012). We were unable to disentangle these two possible interpretations of our findings in the present systematic review.

Also, one of the key issues with animal experiments is the generalizability to humans. For example, it is important to realize that rodents differ from humans in the length of gestation, the lifespan and also in the timing of the development of specific brain regions. Therefore, the animal models included in this review reflect exposure to maternal obesity at a different time of brain development (Semple et al., 2013). Additionally, the included animal models are not able to inform us about the effects of postnatal factors as attachment, abuse and parenting style that are of known importance for children's neurobehavioral development (Loman and Gunnar, 2010). Additionally, in all included studies maternal obesity was induced by diet. We know that other factors, like the amount of physical activity, also play an important role in the development of maternal obesity (Caballero, 2007). Therefore, the animal models used in the included studies may not reflect the human situation of maternal obesity perfectly.

4.3. Strengths, limitations and recommendations

This systematically conducted review has several strengths. First,

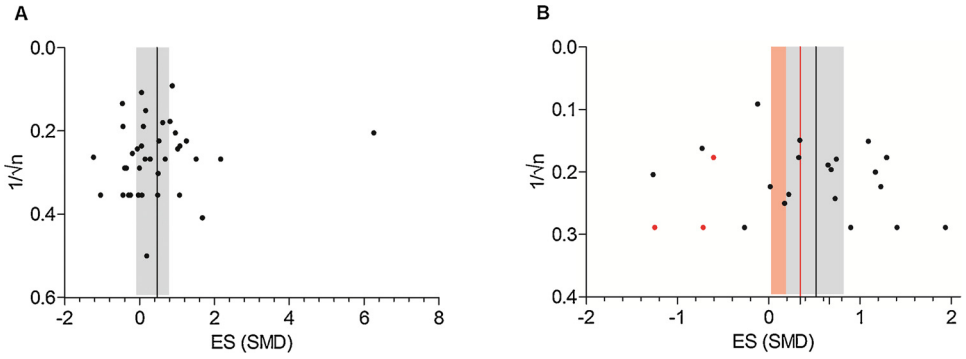

Fig. 5. Filled funnel plots with pseudo 95% confidence limits for locomotor activity (A) and anxiety (B).

we performed an extensive literature search. Second, only the offspring that were fed a normal postnatal diet after weaning were included in the analyses as a control group, to exclude possible moderating effects of offspring's postnatal diet. Third, to answer our research question "Does maternal obesity before and during pregnancy affect offspring's neurobehavior" we purposely selected only those studies where the offspring of the experimental group were exposed to maternal obesity during the entire gestational period. To determine this, weight and/or fat mass of the females had to be reported (to have been measured) and shown to be higher in the experimental group than in the control group from conception onwards. A lack of this information meant that we were unable to determine maternal obesity at conception. Therefore, the downside of this stringent study selection could be that potentially valuable studies were not included in this systematic review. For example, we excluded studies of which the weight/fat mass of the females before pregnancy was not reported to have been measured (e.g. (Rodriguez et al., 2012; Santos et al., 2015)) or, in case it was reported that weight/fat mass had been measured, the details could not be made available to us after directly contacting the authors (e.g. (Camacho et al., 2017)). A different selection strategy may have yielded different results, but investigating this issue was outside the scope of this systematic review.

Second, a limitation is that most of the tests that measured offspring anxiety and memory had different outcomes and there was not one single universally accepted outcome per test. To avoid multiple testing, we defined one primary outcome for each test that we used in our meta-analysis. It is possible that our study results would have shifted in either direction if we had chosen a different primary outcome in our meta-analysis. Reassuringly, the effects of maternal obesity on offspring anxiety and memory pointed into the same direction (Balsevich et al., 2016; Fabian et al., 2015; Bilbo and Tsang, 2010; Thompson et al., 2017), with only one exception (Fernandes et al., 2012) when we looked at the included studies that reported in their study article both our defined primary outcome and other outcomes for anxiety and memory.

Third, we were unable to investigate whether the effects of maternal obesity on offspring activity and anxiety were dependent on the severity of maternal obesity or the nutrient composition in the maternal diet. As both maternal dietary composition and severity of maternal obesity were outside the scope of our review, we cannot rule out the possibility that the effects we found were due to maternal diet and not maternal obesity per se.

Fourth, as in every systematic review, the quality of the review and its conclusion is dependent on the quality of the included studies. The majority of studies included in our review were poorly reported. This is not unique for this field (Avey et al., 2016; Kilkenny et al., 2009; Muhlhausler et al., 2013). Many essential details regarding the methodological design were missing. Consequently, we scored the risk of bias regarding those missing details as unclear. In the absence of mandatory reporting guidelines, we cannot assume that the authors conducted their experiment in an inappropriate way. Not knowing the actual risk of bias of the included studies hampers our ability to draw reliable conclusions. Therefore, the results of this systematic review should be interpreted with caution.

Fifth, we extracted the number (N) of offspring used in the studies. It was frequently unclear in the included studies whether the N referred to litters, individual dams or individual offspring. In that case, we interpreted the N as the number of individual offspring. This means that we may have underestimated the number of offspring for some studies and thereby underestimated the size (i.e. weight) of these studies in our meta-analysis. Moreover, ideally the dams should be the experimental unit instead of the pups. However, it was unclear from the majority of studies which pups belonged to which dam. Thus, although it would have been ideal to use the dam as the experimental unit, we were not able to extract this data.

Sixth, we found evidence for the presence of publication bias for the effect of maternal obesity with offspring anxiety. This finding could imply that publication bias influences the other outcomes in this systematic review, but that we may not have been able to detect this due to the low number of studies included in the analyses. However, the effect of maternal obesity on offspring anxiety was still present after adjusting for the publication bias using the Trim and Fill method (Duval and Tweedie, 2000). Thus our conclusion that maternal obesity before and during pregnancy is linked to an increase in the anxiety behavior of the offspring remains. Moreover, this adjustment should be interpreted with caution, since the Trim and Fill method may inappropriately adjust for publication bias when there is substantial between-study heterogeneity (Terrin et al., 2003; Peters et al., 2007) (although we tried to minimize this risk by using a sample size-based precision estimate (Zwetsloot et al., 2017)).

This systematic review with meta-analyses provides recommendations for future studies. Firstly, we recommend that all scientists conducting animal experiments register their trial (e.g. www.clinicaltrials.eu) in order to decrease the likelihood of publication bias (Jansen of Lorkeers et al., 2014) and publish their experiment according to the available reporting and methodological quality guidelines (Kilkenny et al., 2010; Hooijmans et al., 2010). Secondly, studies must use validated tests to measure offspring neurobehavior as well as report all outcomes that were measured per trial to enhance the transparency and possibility of meta-analysis. Third, future studies should also focus on other species than mice and rats as comparable results in multiple species would increase our confidence in the results and applicability for the clinical situation.

5. Conclusions

This is the first systematic review with meta-analysis of animal studies focusing on maternal obesity before and during the entire pregnancy on offspring neurobehavior. Although the evidence was heterogeneous and the quality of the included studies generally unclear, our results indicate an effect of maternal obesity on increased offspring locomotor activity and anxiety, but not on offspring memory performance. We excluded studies in which maternal obesity was not present before and during pregnancy or in which the presence of maternal obesity was unclear, although these studies may contain additional evidence on the effect of maternal obesity on offspring neurobehavior. The findings of the present systematic review may be important from a public health perspective since obesity is rapidly increasing worldwide, and warrant further research.

Declarations of interest

None.

Funding

This work was supported by a grant of the Dutch Heart Foundation (2013T085) and by a grant of ZonMw (projectnumber 114024105) and DynaHealth H2020 (633595). The funders had no role in the design, conduct and interpretation of the study.

Contributors

RP conceived the study. JL performed the systematic search. MM, CvdB and SM performed the screening and data extraction process. MM performed the analyses with methodological help of CH and KW and drafted the initial versions of the manuscript, which were revised critically by the other authors CvdB, SM, KW, AK, SEO, JL, TR, CH and RP. All authors approved the final version of the manuscript.

Acknowledgments

The authors thank the authors who have provided us information about their study and therefore contributed to the meta-analysis. We also thank Clara Frick (CF) and Eefje van den Nieuwenhof (EN) for their help in the screening and data-extraction phase.

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.neubiorev.2018.12.023.

References

Aburasayn, H., Al Batran, R., Gopal, K., Almutairi, M., Eshreif, A., Eaton, F., et al., 2018. Female offspring born to obese and insulin-resistant dams are not at increased risk for obesity and metabolic dysfunction during early development. Can. J. Physiol. Pharmacol. 96 (1), 97–102.

Adane, A.A., Mishra, G.D., Tooth, L.R., 2016. Maternal pre-pregnancy obesity and childhood physical and cognitive development of children: a systematic review. Int. J. Obes. (Lond.) 40 (11), 1608–1618.

Alvarez-Bueno, C., Cavero-Redondo, I., Lucas-de la, Cruz L., Notario-Pacheco, B., Martinez-Vizcaino, V., 2017. Association between pre-pregnancy overweight and obesity and children's neurocognitive development: a systematic review and meta-analysis of observational studies. Int. J. Epidemiol.

Antoniou, E.E., Fowler, T., Reed, K., Southwood, T.R., McCleery, J.P., Zeegers, M.P., 2014. Maternal pre-pregnancy weight and externalising behaviour problems in pre-school children: a UK-based twin study. BMJ Open 4 (10), e005974.

Avey, M.T., Moher, D., Sullivan, K.J., Fergusson, D., Griffin, G., Grimshaw, J.M., et al., 2016. The devil is in the details: incomplete reporting in preclinical animal research. PLoS One 11 (11), e0166733.

Bahari, H., Caruso, V., Morris, M.J., 2013. Late-onset exercise in female rat offspring ameliorates the detrimental metabolic impact of maternal obesity. Endocrinology 154 (10), 3610–3621.

Balsevich, G., Baumann, V., Uribe, A., Chen, A., Schmidt, M.V., 2016. Prenatal exposure to maternal obesity alters anxiety and stress coping behaviors in aged mice. Neuroendocrinology 103 (3-4), 354–368.

Bellisario, V., Berry, A., Capoccia, S., Raggi, C., Panetta, P., Branchi, I., et al., 2014. Gender-dependent resiliency to stressful and metabolic challenges following prenatal exposure to high-fat diet in the p66(Shc-/-) mouse. Front. Behav. Neurosci. 8, 285.

Bilbo, S.D., Tsang, V., 2010. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. FASEB J. 24 (6), 2104–2115.

Bliddal, M., Olsen, J., Stovring, H., Eriksen, H.L., Kesmodel, U.S., Sorensen, T.I., et al., 2014. Maternal pre-pregnancy BMI and intelligence quotient (IQ) in 5-year-old children: a cohort based study. PLoS One 9 (4), e94498.

Bolton, J.L., Bilbo, S.D., 2014. Developmental programming of brain and behavior by perinatal diet: focus on inflammatory mechanisms. Dialogues Clin. Neurosci. 16 (3), 307–320.

Buffington, S.A., Di Prisco, G.V., Auchtung, T.A., Ajami, N.J., Petrosino, J.F., 2016. Costa-mattioli M. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. Cell 165 (7), 1762–1775.

Caballero, B., 2007. The global epidemic of obesity: an overview. Epidemiol. Rev. 29, 1–5.

Camacho, A., Montalvo-Martinez, L., Cardenas-Perez, R.E., Fuentes-Mera, L., Garza-Ocanas, L., 2017. Obesogenic diet intake during pregnancy programs aberrant synaptic plasticity and addiction-like behavior to a palatable food in offspring. Behav. Brain Res. 330, 46–55.

Caruso, V., Bahari, H., Morris, M.J., 2013. The beneficial effects of early short-term exercise in the offspring of obese mothers are accompanied by alterations in the hypothalamic gene expression of appetite regulators and FTO (fat mass and obesity associated) gene. J. Neuroendocrinol. 25 (8), 742–752.

Chen, Q., Sjolander, A., Langstrom, N., Rodriguez, A., Serlachius, E., D'Onofrio, B.M., et al., 2014. Maternal pre-pregnancy body mass index and offspring attention deficit hyperactivity disorder: a population-based cohort study using a sibling-comparison design. Int. J. Epidemiol. 43 (1), 83–90.

Chin, E.H., Schmidt, K.L., Martel, K.M., Wong, C.K., Hamden, J.E., Gibson, W.T., et al., 2017. A maternal high-fat, high-sucrose diet has sex-specific effects on fetal glucocorticoids with little consequence for offspring metabolism and voluntary locomotor activity in mice. PLoS One 12 (3), e0174030.

Contu, L., Hawkes, C.A., 2017. A review of the impact of maternal obesity on the cognitive function and mental health of the offspring. Int. J. Mol. Sci. 18 (5).

Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.

Dahlhoff, M., Pfister, S., Blutke, A., Rozman, J., Klingenspor, M., Deutsch, M.J., et al., 2014. Peri-conceptional obesogenic exposure induces sex-specific programming of disease susceptibilities in adult mouse offspring. Biochim. Biophys. Acta 1842 (2), 304–317.

Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 56 (2), 455–463.

Edlow, A.G., 2017. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. Prenat. Diagn. 37 (1), 95–110.

Fabian, D., Kubandova, J., Cikos, S., Burkus, J., Fabianova, K., Racekova, E., et al., 2015. The effect of maternal body condition on in vivo production of zygotes and behavior of delivered offspring in mice. Theriogenology 83 (4), 577–589.

Fernandes, C., Grayton, H., Poston, L., Samuelsson, A.M., Taylor, P.D., Collier, D.A., et al., 2012. Prenatal exposure to maternal obesity leads to hyperactivity in offspring. Mol. Psychiatry 17 (12), 1159–1160.

Fernandez-Twinn, D.S., Alfaradhi, M.Z., Martin-Gronert, M.S., Duque-Guimaraes, D.E., Piekarz, A., Ferland-McCollough, D., et al., 2014. Downregulation of IRS-1 in adipose tissue of offspring of obese mice is programmed cell-autonomously through post-transcriptional mechanisms. Mol. Metab. 3 (3), 325–333.

Fernandez-Twinn, D.S., Gascoin, G., Musial, B., Carr, S., Duque-Guimaraes, D., Blackmore, H.L., et al., 2017. Exercise rescues obese mothers' insulin sensitivity, placental hypoxia and male offspring insulin sensitivity. Sci. Rep. 7, 44650.

Flegal, K.M., Kruszon-Moran, D., Carroll, M.D., Fryar, C.D., Ogden, C.L., 2016. Trends in obesity among adults in the United States, 2005 to 2014. Jama 315 (21), 2284–2291.

Gardner, R.M., Lee, B.K., Magnusson, C., Rai, D., Frisell, T., Karlsson, H., et al., 2015. Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: Results from a Swedish total population and discordant sibling study. Int. J. Epidemiol. 44 (3), 870–883.

Garland Jr., T., Schutz, H., Chappell, M.A., Keeney, B.K., Meek, T.H., Copes, L.E., et al., 2011. The biological control of voluntary exercise, spontaneous physical activity and daily energy expenditure in relation to obesity: human and rodent perspectives. J. Exp. Biol. 214 (Pt 2), 206–229.

Godfrey, K.M., Reynolds, R.M., Prescott, S.L., Nyirenda, M., Jaddoe, V.W., Eriksson, J.G., et al., 2017. Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol. 5 (1), 53–64.

Graf, A.E., Lallier, S.W., Waidyaratne, G., Thompson, M.D., Tipple, T.E., Hester, M.E., et al., 2016. Maternal high fat diet exposure is associated with increased hepcidin levels, decreased myelination, and neurobehavioral changes in male offspring. Brain Behav. Immun. 58, 369–378.

Hanson, M.A., Gluckman, P.D., 2014. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol. Rev. 94 (4), 1027–1076.

Hedges, L.V.O.I., 1985. Statistical Methods for Meta-Analysis. New York Academic Press.

Heslehurst, N., Rankin, J., Wilkinson, J.R., Summerbell, C.D., 2010. A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989-2007. Int. J. Obes. (Lond.) 34 (3), 420–428.

Hooijmans, C.R., Leenaars, M., Ritskes-Hoitinga, M., 2010. A gold standard publication checklist to improve the quality of animal studies, to fully integrate the three Rs, and to make systematic reviews more feasible. Altern. Lab. Anim. 38 (2), 167–182.

Hooijmans, C.R., Rovers, M.M., de Vries, R.B., Leenaars, M., Ritskes-Hoitinga, M., Langendam, M.W., 2014. SYRCLE's risk of bias tool for animal studies. BMC Med. Res. Methodol. 14, 43.

Jansen of Lorkeers, S.J., Doevendans, P.A., Chamuleau, S.A., 2014. All preclinical trials should be registered in advance in an online registry. Eur. J. Clin. Invest. 44 (9), 891–892.

Kang, S.S., Kurti, A., Fair, D.A., Fryer, J.D., 2014. Dietary intervention rescues maternal obesity induced behavior deficits and neuroinflammation in offspring. J. Neuroinflammation 11, 156.

Kilkenny, C., Parsons, N., Kadyszewski, E., Festing, M.F., Cuthill, I.C., Fry, D., et al., 2009. Survey of the quality of experimental design, statistical analysis and reporting of research using animals. PLoS One 4 (11), e7824.

Kilkenny, C., Browne, W.J., Cuthill, I.C., Emerson, M., Altman, D.G., 2010. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol. 8 (6), e1000412.

Landry, B.W., Driscoll, S.W., 2012. Physical activity in children and adolescents. PM R 4 (11), 826–832.

Loman, M.M., Gunnar, M.R., 2010. Early experience and the development of stress reactivity and regulation in children. Neurosci. Biobehav. Rev. 34 (6), 867–876.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151.

Moody, L., Chen, H., Pan, Y.X., 2017. Early-life nutritional programming of cognition-the fundamental role of epigenetic mechanisms in mediating the relation between early-life environment and learning and memory process. Adv. Nutr. 8 (2), 337–350.

Moser, V.C., McDaniel, K.L., Woolard, E.A., Phillips, P.M., Franklin, J.N., Gordon, C.J., 2017. Impacts of maternal diet and exercise on offspring behavior and body weights. Neurotoxicol. Teratol. 63, 46–50.

Mouralidarane, A., Soeda, J., Sugden, D., Bocianowska, A., Carter, R., Ray, S., et al., 2015. Maternal obesity programs offspring non-alcoholic fatty liver disease through disruption of 24-h rhythms in mice. Int. J. Obes. (Lond.) 39 (9), 1339–1348.

Muhlhausler, B.S., Bloomfield, F.H., Gillman, M.W., 2013. Whole animal experiments should be more like human randomized controlled trials. PLoS Biol. 11 (2), e1001481.

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., et al., 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 384 (9945), 766–781.

Peters, J.L., Sutton, A.J., Jones, D.R., Abrams, K.R., Rushton, L., 2007. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat. Med. 26 (25), 4544–4562.

Poston, L., Caleyachetty, R., Cnattingius, S., Corvalan, C., Uauy, R., Herring, S., et al., 2016. Preconceptional and maternal obesity: epidemiology and health consequences. Lancet Diabetes Endocrinol. 4 (12), 1025–1036.

Rivera, H.M., Christiansen, K.J., Sullivan, E.L., 2015. The role of maternal obesity in the risk of neuropsychiatric disorders. Front. Neurosci. 9, 194.

Robb, J.L., Messa, I., Lui, E., Yeung, D., Thacker, J., Satvat, E., et al., 2017. A maternal diet high in saturated fat impairs offspring hippocampal function in a sex-specific manner. Behav. Brain Res. 326, 187–199.
Rodriguez, J.S., Rodriguez-Gonzalez, G.L., Reyes-Castro, L.A., Ibanez, C., Ramirez, A., Chavira, R., et al., 2012. Maternal obesity in the rat programs male offspring exploratory, learning and motivation behavior: prevention by dietary intervention pregestation or in gestation. Int. J. Dev. Neurosci. 30 (2), 75–81.
Ruegsegger, G.N., Grigsby, K.B., Kelty, T.J., Zidon, T.M., Childs, T.E., Vieira-Potter, V.J., et al., 2017. Maternal Western diet age-specifically alters female offspring voluntary physical activity and dopamine- and leptin-related gene expression. FASEB J. 31 (12), 5371–5383.
Samuelsson, A.M., Matthews, P.A., Argenton, M., Christie, M.R., McConnell, J.M., Jansen, E.H., et al., 2008. Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming. Hypertension. 51 (2), 383–392.
Samuelsson, A.M., Matthews, P.A., Jansen, E., Taylor, P.D., Poston, L., 2013. Sucrose feeding in mouse pregnancy leads to hypertension, and sex-linked obesity and insulin resistance in female offspring. Front. Physiol. 4, 14.
Sanchez, C.E., Barry, C., Sabhlok, A., Russell, K., Majors, A., Kollins, S.H., et al., 2017. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obes. Rev.
Santos, M., Rodriguez-Gonzalez, G.L., Ibanez, C., Vega, C.C., Nathanielsz, P.W., Zambrano, E., 2015. Adult exercise effects on oxidative stress and reproductive programming in male offspring of obese rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 308 (3), R219–25.
Sasaki, A., de Vega, W.C., St-Cyr, S., Pan, P., McGowan, P.O., 2013. Perinatal high fat diet alters glucocorticoid signaling and anxiety behavior in adulthood. Neuroscience. 240, 1–12.
Sasaki, A., de Vega, W., Sivanathan, S., St-Cyr, S., McGowan, P.O., 2014. Maternal high-fat diet alters anxiety behavior and glucocorticoid signaling in adolescent offspring. Neuroscience. 272, 92–101.
Semple, B.D., Blomgren, K., Gimlin, K., Ferriero, D.M., Noble-Haeusslein, L.J., 2013. Brain development in rodents and humans: identifying benchmarks of maturation and vulnerability to injury across species. Prog. Neurobiol. 106-107, 1–16.
Shalev, U., Tylor, A., Schuster, K., Frate, C., Tobin, S., Woodside, B., 2010. Long-term physiological and behavioral effects of exposure to a highly palatable diet during the perinatal and post-weaning periods. Physiol. Behav. 101 (4), 494–502.
StataCorp, 2017. Stata Statistical Software: Release 15. StataCorp LLC, College Station, TX.
Sullivan, E.L., Nousen, E.K., Chamlou, K.A., 2014. Maternal high fat diet consumption during the perinatal period programs offspring behavior. Physiol. Behav. 123, 236–242.
Sullivan, E.L., Riper, K.M., Lockard, R., Valleau, J.C., 2015. Maternal high-fat diet programming of the neuroendocrine system and behavior. Horm. Behav. 76, 153–161.
Terrin, N., Schmid, C.H., Lau, J., Olkin, I., 2003. Adjusting for publication bias in the presence of heterogeneity. Stat. Med. 22 (13), 2113–2126.
Thompson, J.R., Valleau, J.C., Barling, A.N., Franco, J.G., DeCapo, M., Bagley, J.L., et al., 2017. Exposure to a high-fat diet during early development programs behavior and impairs the central serotonergic system in juvenile non-human Primates. Front Endocrinol (Lausanne) 8, 164.
Tozuka, Y., Kumon, M., Wada, E., Onodera, M., Mochizuki, H., Wada, K., 2010. Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring. Neurochem. Int. 57 (3), 235–247.
Van Lieshout, R.J., 2013. Role of maternal adiposity prior to and during pregnancy in cognitive and psychiatric problems in offspring. Nutr. Rev. 71 (Suppl 1), S95–101.
Vega, C.C., Reyes-Castro, L.A., Bautista, C.J., Larrea, F., Nathanielsz, P.W., Zambrano, E., 2015. Exercise in obese female rats has beneficial effects on maternal and male and female offspring metabolism. Int. J. Obes. (Lond.) 39 (4), 712–719.
White, C.L., Pistell, P.J., Purpera, M.N., Gupta, S., Fernandez-Kim, S.O., Hise, T.L., et al., 2009. Effects of high fat diet on Morris maze performance, oxidative stress, and inflammation in rats: contributions of maternal diet. Neurobiol. Dis. 35 (1), 3–13.
Wright, T., Langley-Evans, S.C., Voigt, J.P., 2011. The impact of maternal cafeteria diet on anxiety-related behaviour and exploration in the offspring. Physiol. Behav. 103 (2), 164–172.
Wu, T., Deng, S., Li, W.G., Yu, Y., Li, F., Mao, M., 2013. Maternal obesity caused by overnutrition exposure leads to reversal learning deficits and striatal disturbance in rats. PLoS One 8 (11), e78876.
Zambrano, E., Martinez-Samayoa, P.M., Rodriguez-Gonzalez, G.L., Nathanielsz, P.W., 2010. Dietary intervention prior to pregnancy reverses metabolic programming in male offspring of obese rats. J. Physiol. (Lond.) 588 (Pt 10), 1791–1799.
Zwetsloot, P.P., Van Der Naald, M., Sena, E.S., Howells, D.W., IntHout, J., De Groot, J.A., et al., 2017. Standardized mean differences cause funnel plot distortion in publication bias assessments. eLife 6.