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Metabolic and behavioural effects in offspring exposed to maternal sucrose consumption: a systematic review and meta-analysis of data from rodent models

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Original Article

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Abstract

Consumption of sugar-sweetened beverages (SSBs) during pregnancy has been associated with childhood obesity. Research in which rodent dams have been given high-fat/high-sugar diets has consistently found metabolic alterations in their offspring. However, what remains unclear is the potential impact on the developing fetus of giving sugar in isolation at concentrations similar to SSBs to the mothers. Therefore, we conducted a systematic review and meta-analysis (Protocol No: 127115 on Prospero) to identify potential relationships between maternal sucrose consumption and metabolic outcomes in offspring of rodent (rat or mouse) models. We analysed studies that provided rodent mothers dams with access to sucrose solutions (8–20% w/v) prior to conception, during pregnancy and/or lactation and that reported offspring outcomes of body weight (BW), body composition and glycaemic control. Following a systematic search of four databases (PubMed, EMBASE, Web of Science and Scopus) performed on 15 January 2019, maternal and offspring data from 15 papers were identified for inclusion. Only rat studies were identified. Meta-analyses were performed on standardised mean differences for maternal and offspring BW and fasting glucose levels, with subgroup analyses of strain, sucrose concentration, exposure period and sex of offspring. A bias towards the inclusion of only data from male offspring was identified and this limited interpretation of potential sexually dimorphic outcomes. Maternal sucrose exposure was associated with an increased risk of obesity and poor glucose disposal in adult and aged offspring.

Introduction

Obesity is a significant health challenge facing modern society. The World Health Organisation has reported that prevalence has nearly tripled over the last 40 years.[1] With an estimated 1.9 billion people considered overweight or obese globally, the social and financial burdens of this epidemic are staggering.[1,2] In part, obesity has been attributed to the consumption of added sugars, with the greatest source from sugar-sweetened beverages (SSBs).[3] Epidemiological studies have found that consumption of added sugars is associated with obesity, type 2 diabetes and cardio-metabolic disease.[4-8] However, what is less well understood is the potential influence added sugars may have on the developing fetus during early life.

There is a growing recognition that the origins of obesity begin *in utero*; extensive research has consistently shown an increased risk of childhood obesity when the mother is overweight or obese[9,10] or consumes a high-fat diet.[11-13] This intergenerational link may be a factor in the amplification of the obesity epidemic.[14] Dysregulation of gene expression through DNA methylation, histone modification and mitochondrial dysfunction has been reported in obese offspring.[15,16] Whether excessive maternal sugar consumption is involved in these mechanistic links remains unclear.

Three recent epidemiological studies have found an association between maternal SSBs consumption during pregnancy and childhood adiposity.[17-19] Specifically, body mass index and fat mass were higher in children and infants under 7 years of age, independent of the child's SSBs intake. This association was stronger when mothers consumed SSBs during the second trimester.[17] However, such studies are inevitably subject to a range of confounding factors that limit their ability to identify causality. Because they can eliminate confounds, animal models have advanced our understanding of the biological mechanisms involved in maternal overnutrition,[20,21] including high-sugar diets.[22] Given SSB intake is a prime target for the prevention of excessive weight gain during pregnancy, it is important to validate the epidemiological findings[17-19] in animal models. Evidence from some rodent studies where dams were fed sucrose as part of a solid food diet during pregnancy has reported impaired metabolism in their

offspring. These impairments have included increased body weight (BW), adiposity, hyperglycaemia, insulin resistance and altered hepatic lipid metabolism.[23-25] The translational value of these experiments is limited because the sucrose content (up to 65% of energy intake) was much higher than what humans normally consume. Thus, a more appropriate animal model for human SSB consumption during pregnancy would be the manipulation of the maternal diet with sucrose administered in solution.

The research included in the present review was confined to studies in which dams were provided with sucrose solutions at concentrations more comparable to those found in commercially available SSBs (8–20% w/v). We sought to determine whether sucrose consumption at this concentration alters offspring metabolism. The main aim was to identify possible relationships between maternal intakes of sucrose solutions and offspring outcomes for BW, body composition and glycaemic control. A secondary aim was to assess whether maternal sucrose consumption during pregnancy affects their offspring's consumption patterns.

Materials and methods

This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2009) Guidelines (Supplementary Table S1). The protocol was developed with the SYstematic Review Centre for Laboratory animal Experimentation's (SYRCLE) Protocol template, Version 2.0[26] and registered on Prospero on the 18th March 2019 (Protocol number: 127115; available from https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=127115) and Camarades NC-3R Systematic Review Facility (http://syrf.org.uk/protocols/).

Search strategy and study selection

The following databases were searched from inception to 15 January 2019: PubMed, EMBASE via OvidSP, Web of Science and Scopus. The extensive search strategy used keywords, medical subject headings (MeSH), EMTREE terms and related synonyms based on maternal sucrose feeding and fetal development. Previously published animal filters[27,28] were adapted to identify rodent (rat and mouse) papers and used in the final search sets for PubMed and EMBASE. No animal filters were used for Web of Science and Scopus as they are currently not available. The final search strategy for each database can be found in Supplementary Table S2. Extracted publications were combined and duplicates manually removed in Endnote reference management software (EndNote™ X8).

Papers were screened by two independent reviewers, according to pre-defined exclusion criteria. Based on title and abstract, papers were excluded if they were non-experimental, non-rodent, genetically bred or metabolically compromised rodent models, non-interventional during pregnancy or lactation or if they reported fetal but no offspring outcomes. Further exclusion criteria were applied to full-text screening. We then further excluded papers with no appropriate control, isocaloric pair-feeding models, high-fat diets (>15% total energy content), protein/calorie restricted diets, intragastric or intraperitoneal feeding models or if sucrose was administered as a solid component of the diet (i.e. chow component). Only papers providing dams with a sucrose solution with a concentration between 8 and 20 % w/v were included. No restriction was placed on publication date, but only English papers were included. Hand screening of references lists was performed to identify further publications.

Data extraction

We extracted bibliographical (author, year, title) and methodological information (experimental conditions, maternal and offspring sample size, unit of analysis) from eligible papers. Data on animal characteristics (species, strain, age, weight, offspring sex, litter standardisation), sucrose feeding (exposure timing: during pre-conception and/or pregnancy and/or lactation; concentration/s; compulsory or voluntary administration), maternal and offspring metabolic (bodyweight, body composition, glycaemic control) and behavioural outcomes (food/fluid intake and preference behaviours) were also extracted. In cross-fostering models, data were extracted for each experimental group. Outcome measures were collected as mean and standard error of mean (S.E.M.) or standard deviation (S.D.), as reported in the publications. If required, a digital ruler (Pixel Ruler version 3.1) was used for extracting graphical data. A second reviewer checked 5% of the extracted data for errors and discrepancies were corrected based on the original text. Attempts to contact the author were made if data were not available or further information was required.

Meta-analysis

The main outcome measures included for meta-analyses were maternal and offspring BW and fasting glucose levels (FGLs). Random effects meta-analyses were performed using R Studio Statistical Package, Version 3.5.1 (2018-07-02) 'Feather Spray' for standardised mean differences (SMD) and corresponding 95% confidence intervals. The *metacont* function from the *meta* package was used for standard analyses. The *rma* function from the *metafor* package was used for the meta-regression. Papers containing different interventional groups of animals,[29] including those using cross-fostering models,[30,31] were included as separate data sets and thus effectively treated as independent experiments. For studies that compared more than one data set to the same control group, a correction was made using the following equation: $N_{\text{corrected control}} = N_{\text{control}}/\text{no. of experimental groups}$.[32] The I^2 statistic was used to assess heterogeneity.

Data for maternal BW (~PND21) and data for maternal FGL (taken between pre-conception and PND21) were extracted, and separate meta-analyses were performed for these outcomes. All dams were exposed to a minimum of 4 weeks' sucrose feeding. Offspring BW data were extracted in the pre-weaning period (PND15–28) and adulthood (PND56–504). Offspring analyses included rodents exposed to sucrose prior to mating and/or post mating (i.e. pregnancy or pregnancy and lactation); however, rodents exposed to sucrose only during the lactation period (through a cross-fostering model) were excluded to analyse *in utero* effects. Offspring provided direct access to sucrose solution post-weaning were also excluded. Sub-group analyses were conducted on maternal and offspring data for sucrose concentration, strain and on sex in offspring outcomes. In addition, a sub-group analysis, separated by pre and post mating sucrose exposure, was performed on offspring BW to eliminate confounding effects of the maternal metabolic state. Meta-regression analysis was also performed to analyse the effect of offspring age on BW during adulthood. All data are presented as forest plots drawn using the forest function from the *metafor* package. Four papers included in this review were excluded from the meta-analysis for the following reasons: (i) no sample size reported; (ii) insufficient statistical reporting and (iii) insufficient data for pre-weaning or adult time points.

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Study quality assessment

A comprehensive assessment of methodological quality was performed using the SYRCLE's Risk of Bias (RoB) Tool.[33] Adapted from the Cochrane RoB Tool,[34] it has been specifically designed for use in systematic reviews of animal models to assess internal validity. Briefly, the checklist relates to five categories of bias: selection (items 1–3), performance (items 4–5), detection (items 6–7), attrition (item 8), reporting (item 9) and with the final item relating to litter as the unit of analysis (item 10). Due to multiparous births in rodents, using the individual pup as an experimental unit rather than litter increases the chance of Type 1 errors and as such may cause unjustly inflated precision. Items were judged as 'low' risk of bias, 'high' risk of bias or 'unclear' if we were unable to clearly assign risk of bias. Two independent reviewers (HLM and CHL or HLM and RA) assessed the included publications, with discrepancies resolved by discussion.

In addition, all papers were assessed for reporting quality by adherence to the Animal Research: Reporting of in Vivo Experiments (ARRIVE) Guidelines Checklist.[35] Developed by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) to improve reporting standards in animal publications, our assessment aimed to identify specific areas of poor reporting to aid in evaluating the reliability of each paper. We modified and developed the ARRIVE Guidelines into evaluation descriptors and a reporting system (Supplementary Table S3). The 20-item checklist was extended to include 40 associated sub-items relevant to this review. Items and sub-items are described as fully reported (FR), partially reported (PR) or non-reported, similar to previously reported tools.[36,37]

Results

Study selection

Our initial database search identified 4678 papers for review. Following removal of duplicates (2219 papers), a total of 2459 papers were screened based on eligibility criteria applied to title and abstract (2181 papers excluded) and full text (263 papers excluded). Searching of reference lists did not yield any further inclusions. Fifteen papers (including 16 maternal groups and 19 offspring groups) of maternal sucrose exposure were identified for final inclusion in this systematic review (see Fig. 1). A full list of the 263 excluded papers in Phase 2 and reason for exclusion can be found in Supplementary Table S4.

Study characteristics and design

Although several terms for mice were included in the database search, only rat studies were identified. Eleven of the included papers used Sprague-Dawley rats,[31,38-47] three used Wistar rats[30,48,49] and one did not report strain type.[29] Sucrose was administered at either 10% w/v[29-31,48,49] or 20% w/v[29,38-47] and maternal exposure ranged from 16 to 126 days, including periods during pre-conception, gestation and lactation. The majority[29,30,32-47] employed a compulsory drinking paradigm with sucrose solution being the only source of drinking fluid. A voluntary consumption model was used in two papers, with sucrose offered in addition to drinking water.[31,48] In all papers, offspring were weaned on to chow and water. They remained on this standard diet until the end of experimental testing, except for one study.[48] Here male offspring aged ~13 weeks old were given direct access to chow and 10% sucrose solution for seven weeks. This data set was not included in offspring meta-analyses to avoid confounding the results. Study designs for maternal sucrose interventions can be found in Supplementary Table S5. A cross-fostering model was used in two papers, giving rise to three additional offspring groups.[30,31] Full details of extracted study characteristics can be found in the Supplementary Table S6.

For each study, the chow component of the diet was identical between control and treatment groups; therefore, the only difference was availability of sucrose in drinking fluid. Macronutrient composition of control diet was not always reported,[29,41,44,46,47] and, for the papers that included this information, variations were noted in energy content for fat (range 4% to 13.5%), carbohydrate (39.1% to 60%) and protein (19.3% to 28.5%). Total energy content was similar between reported chows (~ 3 to 4 kcal/g). A full breakdown of reported chow composition can be found in the Supplementary Table S7.

Maternal outcomes

A summary of maternal outcomes is presented in Table 1. Ten of the included papers reported maternal results for bodyweight, body composition, glycaemic control and consumption. Due to variations in experimental design between studies, data were not available for all of the maternal outcomes listed in Table 1.

Maternal BW and body composition

Maternal BW data were extracted from seven experimental groups.[29,31,43,45,48,49] No significant change was reported for BW in dams measured during gestation (GD21),[45] lactation (PND21)[31] or both time-points.[43,48,49] Two data sets from one study observed a significant increase in BW at PND21 when dams were fed 10% or 20% w/v sucrose during pregnancy and lactation.[29] A meta-analysis on six of the extracted data sets measured at PND21 did not show a significant effect on maternal BW from sucrose consumption (SMD = 0.76, 95% CI -0.21, 1.73, $I^2 = 77\%$), as seen in Fig. 2. Body composition in dams was seldom reported, with fat mass described in only three papers. Fat mass was assessed either directly by the Soxhlet method for total body fat content[38] or by resection of fat pad deposits[48,49] or, indirectly, by plasma leptin concentration.[49] Increased total body fat was observed in dams fed sucrose for 18 weeks from pre-conception to lactation.[38] Increased visceral and subcutaneous adipose tissue in dams fed from 4 weeks pre-conception to lactation was noted, although leptin concentration did not differ between sucrose fed dams and control dams.[49] Conversely, no significant difference was identified in retroperitoneal fat pad analysis during a shorter 10-week intervention, commencing four weeks pre-mating and ceasing at parturition.[48]

Maternal FGLs, glycaemic control and triglycerides

Maternal intervention groups received a minimum of 4 weeks' access to sucrose solutions and data were obtained for FGL in 10 experimental groups. Two data sets were taken prior to mating,[30,48] five during pregnancy[40-42,45,46] and three at the end of lactation.[29,43] Meta-analysis identified a significant increase in FGL in dams exposed to sucrose relative to control dams (SMD = 1.61; 95% CI = 0.78, 2.44; I^2 = 80%), as shown in Fig. 3a. When concentration was taken into consideration, no effect was evident in 10% w/v solutions (SMD = 0.43; 95% CI= -0.68, 1.53; I^2 = 76%), whereas 20% solutions resulted in a significant elevation in maternal FGL, with low heterogeneity

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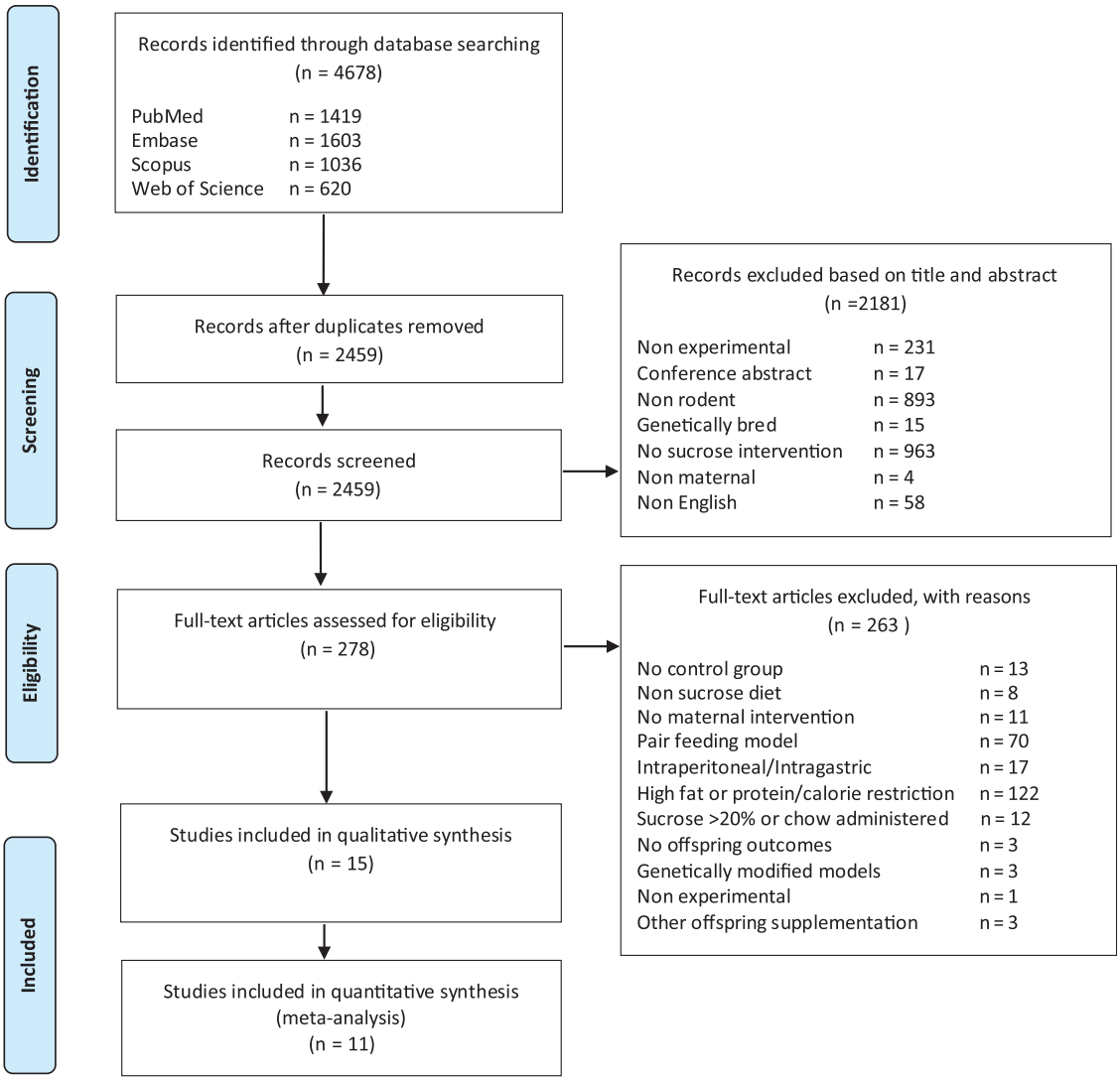

Fig. 1. PRISMA flow.

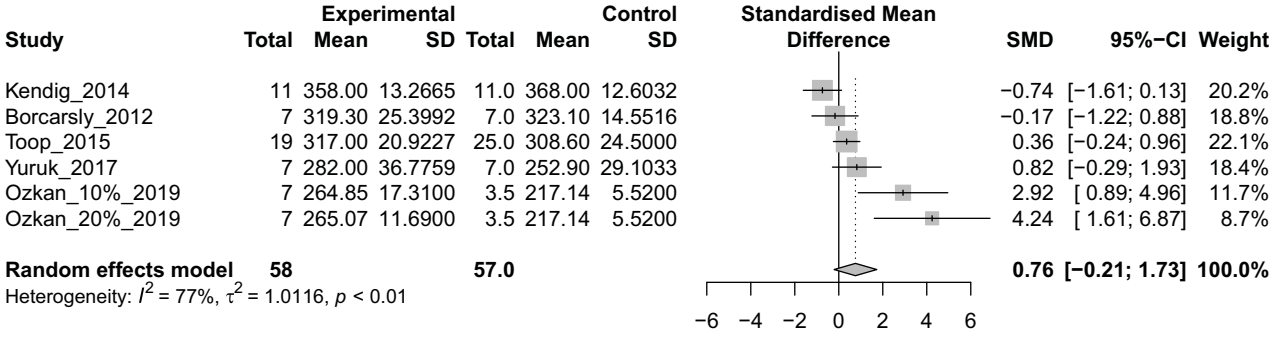

Fig. 2. Maternal body weight.

(SMD = 2.02; 95% CI = 1.51, 2.52; I^2 = 0%), see Fig. 3b. As for strain, although Wistar rats showed no significant effect (SMD = -0.07; 95% CI= -0.85, 0.71; I^2 = 56%), FGL was significantly elevated in Sprague-Dawley rats (SMD = 2.05; 95% CI = 1.51, 2.59; I^2 = 4%); see Fig. 3c. Two data sets did not report strain type.[29] It is worth noting that both studies using Wistar rats provided sucrose concentrations of 10% w/v, thus making it impossible to determine whether these failures to detect an effect of sucrose consumption on FGL were due to concentration or strain.[48,49]

Maternal fasting insulin was reported in four data sets, with three observing a significant increase relative to control[29,43], whereas one found no change.[49] Two papers reported dynamic assessment of maternal glycaemic control through glucose tolerance tests (GTT).[48,49] Reduced glucose disposal was observed following

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Table 1. Summary of maternal characteristics and outcome measures of included studies. Reported outcomes extracted include maternal bodyweight prior to mating, during pregnancy and lactation, fasting blood glucose and insulin levels and consumption data

					Summary of Maternal Findings: Effect of Sucrose Exposure Relative to Control in Dams						
					Bodyweight			FBGL	FPI		
Citation	Sucrose Concentration (% w/v)	Rat Strain	N	Age at Conception (days)	Conception	GD21	PND21	(PC, G, L)	(PC, G, L)	Food Intake	Fluid Intake
Ozkan (2019)	10 20	NR NR	7 7	PND84 PND84	– –	– –	Significant ↑↑ Significant ↑↑	Significant ↑ (L)† Significant ↑ (L)†	Significant ↑ (L)† Significant ↑ (L)†	– –	Significant ↓ Significant ↓
Kisioglu (2018)	20	SD	5-7	PND119	–	–	–	–	–	Significant ↑	No effect
Zhang (2018)	20	SD	6	–	–	–	–	Significant ↑(G)	–	–	–
Feng (2017)	20	SD	20	–	–	–	–	Significant ↑ (G)	–	No effect (DNP)	No effect (DNP)
Gu (2017)	20	SD	10	PND70–84	–	–	–	Significant ↑(G)	–	–	–
He (2017)	20	SD	11	–	–	–	–	–	–	–	–
Toop (2017)	10	WS	19	PND84	–	–	–	–	–	–	–
Yuruk (2017)	20	SD	5-7	PND98	No effect	No effect	No effect	Significant ↑(L)	Significant ↑ (L)	Data*	Data*
Wu (2016)	20	SD	NR	PND140	–	–	–	–	–	–	–
Kendig (2014)	10	WS	11	PND91–98	No effect	No effect	No effect	No effect (PC)	–	Significant ↓	Significant ↑
Toop (2015)	10	WS	19	PND91	No effect (DNP)	No effect (DNP)	No effect	No effect (PC (L)	No effect (L)	Significant ↓	Significant ↑
Kuang (2014)	20	SD	10	–	–	–	No effect	Significant ↑ (G)	–	No effect	No effect
Wu (2014)	20	SD	8	–	–	–	–	Significant ↑ (G)	–	–	–
Bocarsly (2012)	10	SD	5	–	–	–	–	–	–	–	–
Wu (2011)	20	SD	8	–	–	–	–	–	–	–	–

DNP – data not provided; FBGL – fasting blood glucose levels; FPI – fasting plasma insulin; G – gestation; GD21 – gestational day 21 (last day of pregnancy); L – lactation; N – sample size; NR – not reported; PND – postnatal day; PC – pre-conception; PND21 – postnatal day 21 (last day of lactation); SD – Sprague-Dawley; WS – Wistar; % w/v – concentration percentage weight per volume; – outcome not measured; ↑increase; ↓decrease; † data measured at PND28; * graphical data provided but unable to determine statistical effect.

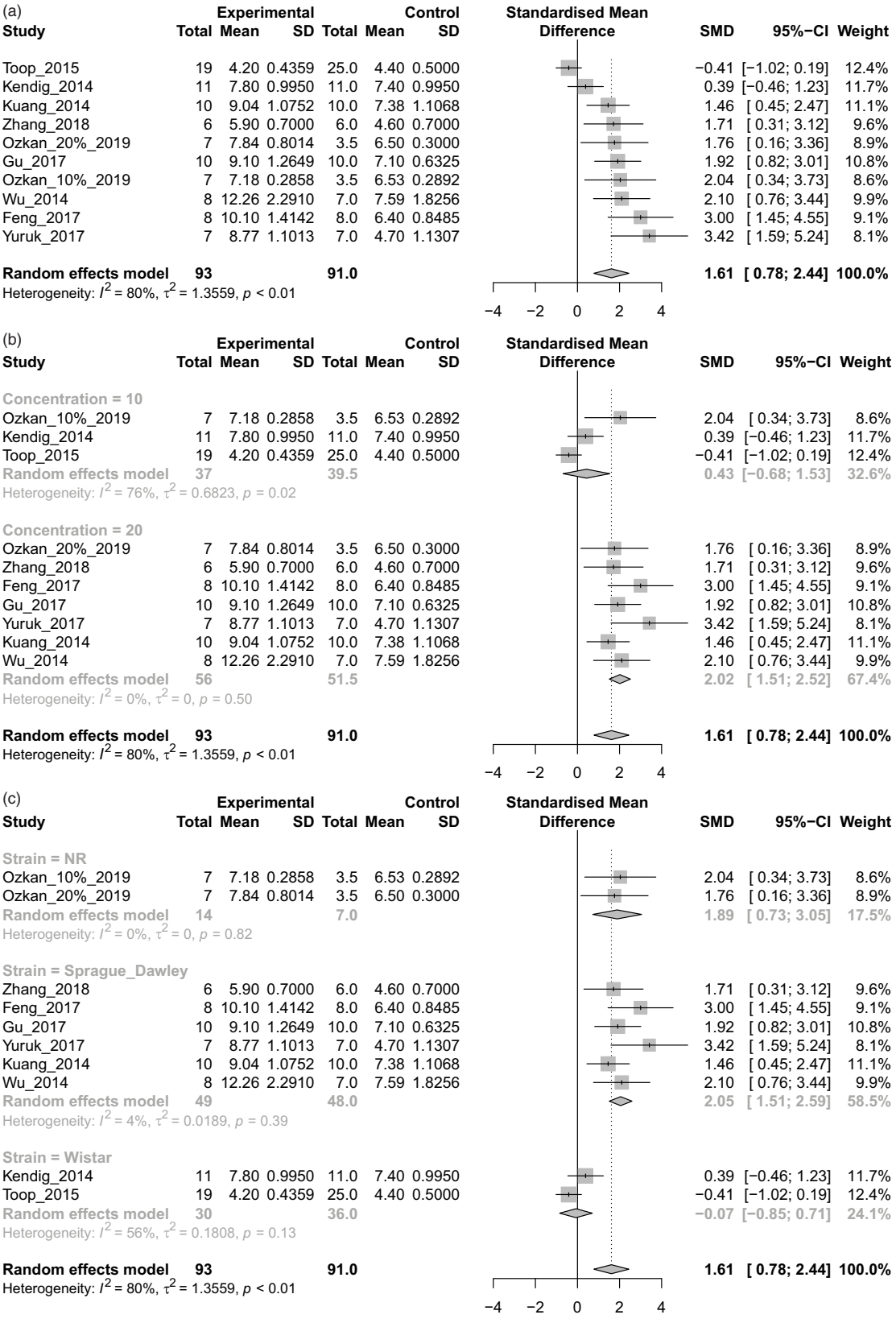

Fig. 3. (a) Maternal BGL. (b) Maternal BGL concentration. (c) Maternal BGL.

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either oral[48] or intraperitoneal[49] administration of a glucose load, thus suggesting glucose intolerance. In both cases, this was measured just prior to conception, following 4 weeks of sucrose exposure. However, subsequent intraperitoneal GTT, performed at the end of lactation, observed an amelioration of this effect.[49]

Two data sets provided plasma triglyceride (TG) concentrations.[48,49] One identified a significant increase at the pre-conception time point[48] and one observed no change at the end of lactation.[49]

Maternal food and fluid intake

Significant variation in consumption was evident in eight data sets reporting maternal food and fluid intakes during the intervention period.[29,40,45,48,49] Sustained increases in sucrose solution intake compared to water were found in two groups, with a compensatory reduction of chow intake[48,49]. Other studies reported either reduced fluid intake,[29] an increase in food intake with no change in fluid[38] or no change in food or fluid intake relative to control dams.[40,45]

Relationship between maternal sucrose consumption and offspring BW and body composition

The relationship between maternal sucrose consumption and BW in pre-weaning and adult rats was not uniform across papers (Table 2). Substantial increases in offspring BW during the pre-weaning period, defined as PND1–28, were found in some studies,[29,39,45] whereas no effect was found in others[30,48] or even a significant reduction.[31] Overall, the meta-analysis on 13 experimental data sets from seven papers identified a minor elevation in pre-weaning BW (SMD = 0.81; 95% CI= 0.06, 1.57; I^2 = 81%), although significant heterogeneity was present (see Fig. 4). Further exploration by subgroup analysis showed an increase in pre-weaning BW of animals when the males and females were analysed together, compared to males and females analysed separately. An increase was also seen in rats of unknown strain compared to Sprague-Dawley and Wistar rats. It should be noted, the two data sets that did not report strain were extracted from the same publication.[29] No effect was detected on pre-weaning offspring BW for concentration. See Supplementary Fig. S8 for sub-group analysis.

BW data were available for 323 adult offspring. When maternal sucrose consumption and the impact on BW in adult offspring rats were analysed, a significant increase in BW (SMD = 0.47; 95% CI= 0.13, 0.81; I^2 = 36%) (Fig. 5a) was found with low heterogeneity. Further exploration by subgroup analysis did not show a clear effect of sex or concentration, but the increase in BW may be specific to Sprague-Dawley rats or when dams were exposed to sucrose post conception rather than prior to mating (Fig. 5b-e). Variability in the timing of BW measurement ranged from 56 to 504 days of age and, according to meta-regression modelling, the effect on BW did not depend on age, $p = 0.5944$.

Only two papers reported data on adiposity of offspring, assessed directly by resection of fat pads[30] or total body fat[38,] and their results differed. Toop *et al.*[30] reported decreases in female retroperitoneal fat mass and male total fat mass in 12-week-old rats exposed to maternal sucrose consumption during a 4-week pre-conception period, pregnancy or lactation. In contrast, Kisioglu *et al.*[38] observed an increase in offspring total body fat at the end of weaning. Although in this study, maternal sucrose exposure was significantly longer, starting 12 weeks prior to conception and finishing at the end of lactation. Furthermore, the data were not separated by sex.[38]

Relationship between maternal sucrose consumption and offspring FGLs, glycaemic control and TGs

Twelve papers provided data for fasting blood or plasma glucose concentration in offspring measured between the pre-weaning and adult period (Table 3). Thirteen experimental data sets were included in the general meta-analysis in adult offspring measured at PND84–616, with no effect observed (SMD = 0.32; 95% CI= −0.18, 0.82; I^2 = 55%); see Fig. 6. Seven of these papers provided additional data on glucose control, as indicated by static assessment of fasting plasma insulin levels,[29,30,39,43,49] Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR)[39,42,43] and QUICKI estimates[43,48] or by dynamic assessment of whole body glucose tolerance through intraperitoneal[30,39,42] or oral[48] GTT. There was no significant effect on glucose disposal in offspring exposed to maternal sucrose consumption compared to control offspring aged 3 weeks,[30,43] 12 weeks[30] and approximately 13 weeks old.[48] In one study where male offspring who presented with a normal oral GTT at 13 weeks and were subsequently were offered sucrose for the following seven weeks, their QUICKI Index was elevated compared to controls.[48] Further evidence for metabolic programming in male offspring was provided by Zhang *et al.*[39], who reported hyperglycaemia at the 30-min time point during an intraperitoneal GTT in 4-month-old rats; however, HOMA-IR levels were unchanged. When intraperitoneal GTT was retested at 6 months of age, there was no longer any effect. Furthermore, He *et al.*[42] observed hyperglycaemia after 30-min during an intraperitoneal GTT, hyperinsulinaemia and elevated HOMA-IR levels for aged offspring (22 months).

Only four papers reported data on liver and/or plasma TG concentrations.[30,31,39,43] Due to limited data, a meta-analysis could not be conducted. No effect was observed in plasma and/or liver TGs in rats aged PND21 to PND180.[30,31,39] In contrast, Yuruk *et al.*[43] reported significantly higher levels for blood and liver TG concentrations measured at weaning. A full summary of offspring glycaemic outcomes is shown in Table 3.

Relationship between maternal sucrose consumption and offspring food and fluid intake

Food and fluid intake was seldom reported in offspring outcomes. Four papers reported no significant change in chow consumption for offspring exposed compared to control offspring.[30,39,42,48] Similarly, water consumption did not differ between groups, as reported in two papers[39,42] and a third observed no significant difference in sucrose consumption when 13-week-old males were given *ad libitum* access to 10% w/v sucrose for 7 weeks.[48]

Study quality assessment

Risk of bias

Results from the assessment of risk of bias are presented in Table 4. The results are presented for individual papers, and each item was assigned either low risk, high risk or unclear risk. In summary, risk of bias for the majority of papers was judged unclear. Questions 1–3 related to selection bias attributed to a lack of randomisation, baseline characteristics or concealment. Twelve of the included papers reported randomising animals to groups, yet failed to

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Table 2. Summary of offspring anthropometric outcome measures. Reported outcomes extracted include offspring bodyweight at birth, the pre-weaning period and adulthood. Also included were body composition outcomes

					Summary of Offspring Anthropometric Measures: Effect of Sucrose Exposure Relative to Control			
					Bodyweight			
Citation	Rat strain	Sucrose concentration (% w/v)	Sucrose exposure	N	Birthweight	Weaning (PND1–28)	Adulthood (PND 112–504)	Body Composition
Ozkan (2019)	– –	10 20	Dams during gestation and lactation Dams during gestation and lactation	14 14	–	Significant ↑ (mixed sex) Significant ↑ (mixed sex)	– –	–
Kisioglu (2018)	SD	20	Dams 12 weeks pre-conception, pregnancy and lactation	5–7	–	–	–	Significant ↑ Measured by soxhlet technique at PND21
Zhang (2018)	SD	20	Dams during pregnancy	8–10	Significant ↑	Significant ↑	No effect ♂ (PND28–112)	–
Feng (2017)	SD	20	Dams during pregnancy	8–12 ♂	Significant ↑♂	–	No effect ♂ (PND112)	–
Gu (2017)	SD	20	Dams during pregnancy	10 ♂	Significant ↑♂	–	Significant ↑♂ (PND140)	–
He (2017)	SD	20	Dams during pregnancy	11 ♂	–	–	Significant ↑ ♂ (aged 18mths)	–
Toop (2017)	WS	10	Dams 4 weeks pre-conception, pregnancy and/or lactation∞	8 ♂ 8 ♀	–	No effect ♀[a,b,c] No effect ♂[d,e,f]	No effect ♂, ♀	Significant ↑visceral fat in ♀[a] (PND21) Significant ↓ retroperitoneal fat in ♀[b] (PND84) Significant ↓ total fat, visceral, gonadal and omental fat in ♂[c] (PND84)
Yuruk (2017)	SD	20	Dams 12 weeks pre-conception, pregnancy and lactation	5–7	No effect (mixed sex)	Significant ↑ (mixed sex)	–	–
Wu (2016)	SD	20	Dams during pregnancy	6 ♂	–	–	–	–
Kendig (2014)	WS	10	Dams 4 weeks pre-conception, pregnancy and lactation	11 ♂ 11 ♀	No effect ♂, ♀ (n=10/sex)	No effect ♂, ♀ (PND1–21)	No effect ♂, ♀ (PND56–94)	–
Toop (2015)	WS	10	Dams 4 weeks pre-conception, pregnancy and lactation	15 ♂ 15 ♀	No effect ♂, ♀	–	–	–
Kuang (2014)	SD	20	Dams during pregnancy	10 ♂	–	Significant ↑ ♂ (PND28)	Significant ↑ ♂ (PND56)	–
Wu (2014)	SD	20	Dams during pregnancy	8	Significant ↑	–	No effect ♂ (PND140)	–
Bocarsly (2012)	SD	10	Dams during pregnancy (GD6-21) and/or lactation∞	12 ♂ 12 ♀	–	Significant ↑ ♂[c,d] Significant ↓ ♀[b] (PND15)	Significant ↑♂[c,d] Significant ↑♀[a,b] (PND180)	–
Wu (2011)	SD	20	Dams during pregnancy		No effect ♂, ♀	–	No effect ♂ (PND140)	–

GD – gestational day 21; N – sample size; NR – not reported; PND – postnatal day; PC – pre-conception; PND – postnatal day; SD – Sprague-Dawley; WS – Wistar; % w/v – concentration percentage weight per volume; – outcome not measured; ↑ – increase; ↓ – decrease; ♂ - male; ♀ - female.
[a]In female interventional group exposed to sucrose during gestation period only (cross-fostering model).
[b]In female interventional group exposed to sucrose during lactation period only (cross-fostering model).
[c]In female interventional group exposed to sucrose during gestation and lactation periods (cross-fostering model).
[d]In male interventional group exposed to sucrose during gestation period only (cross-fostering model).
[e]In male interventional group exposed to sucrose during lactation period only (cross-fostering model).
[f]In male interventional group exposed to sucrose during gestation and lactation (cross-fostering model).
∞ Cross-fostering model.

adequately describe the methods (e.g. random number generator) and therefore were judged unclear. Three papers failed to describe randomisation at all.[29,31,43] Dam age and weight at the commencement of the study were considered necessary to determine whether groups were comparable, yet only six papers reported both (Q2). Concealment of the investigator to group allocation (Q3) was not reported by any papers (0/15). Similarly, randomisation of housing (0/15 papers) and blinding of caregivers (1/15 papers) were poorly

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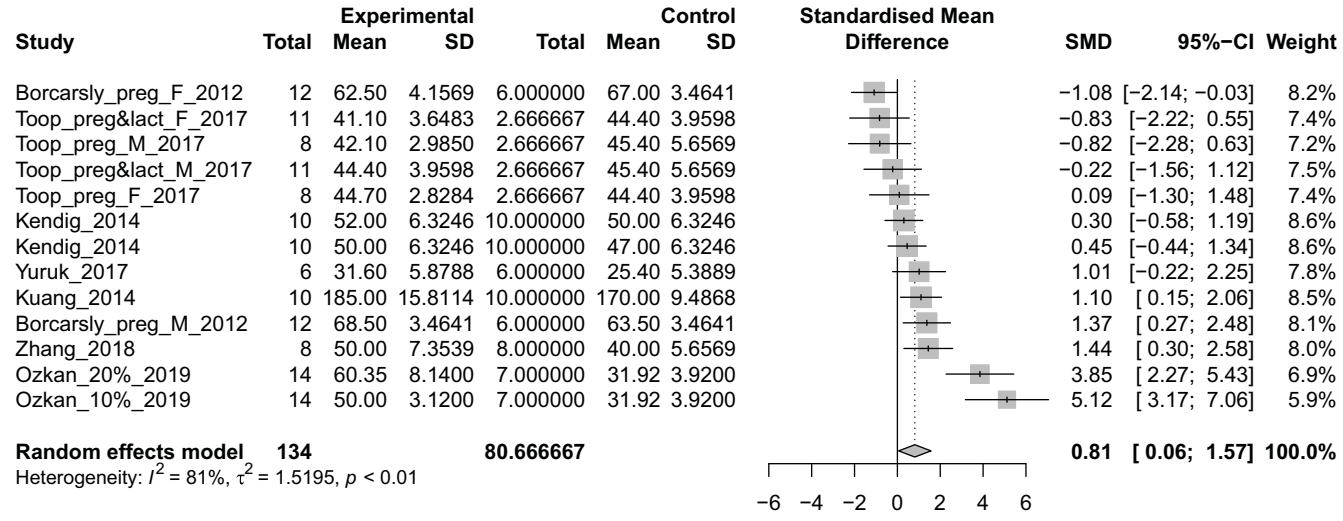

Fig. 4. Offspring body weight weaning.

performed. For detection bias, two papers reported randomly selecting animals for outcomes assessment (Q6) and blinding the assessor during outcome measurements (Q7). Data exclusion due to adverse events was addressed in three papers (Q8). The majority of studies (13/15) were assessed as free of selective outcome reporting by comparing methods and results within the paper (Question 9). Litter as a unit of analysis was considered if either (a) one animal was randomly selected to represent the litter including situations where one animal of each sex was used, (b) litter mean was used for analysis or (c) if litter was a random factor in mixed models analysis. Only five papers were judged free of using incorrect unit of analysis causing unjustly inflated precision (Q10).

Reporting adherence to ARRIVE guidelines checklist

The percentage of studies fully, partially or not reporting the 20-item checklist can be seen in Supplementary Fig. S9. In general, we observed low to moderate adherence to the guidelines for the included papers. Four items were assessed as 100% FR, including title, ethical statement, defining experimental outcomes in methods and reporting of each analysis with a measurement precision. Reporting of the abstract and background were judged as PR if the descriptor was not fully met (FR 47%; PR 53%). This was commonly observed when papers did not report species, strain or background summary in the abstract and human relevance in the introduction. Study design was not well reported (100% PR) due to an absence of blinding and reporting of litter or individual animal as unit of analysis. All papers PR detail on housing and husbandry (100% PR), with cage, bedding and housing type frequently omitted. Only two papers fully described sample size by inclusion of calculation or power analysis (13% FR; 73% PR; 13% NR). The majority of papers did not report adequate randomisation techniques and allocation to treatment groups (13% PR; 87% NR). Many failed to include testing for normality in statistical analyses (33% FR; 60% PR; 7% NR). Baseline data required for this review were maternal age and weight, with 5 out of 15 papers reporting both. Study limitations were described occasionally; however, no paper discussed scientific implications of their findings for the 3R's in animal research (100% PR), and translation to human populations was considered in just over half the included papers (53% FR; 47% NR). Individual study assessment for adherence to ARRIVE guidelines can be found in Supplementary Table S10.

Discussion

The purpose of this systematic review and meta-analysis was to identify relationships between maternal sucrose consumption and the metabolic health in offspring. Importantly, for high translational relevance, we included maternal dietary interventions where sucrose concentration closely resembled that of SSBs consumed by humans. In total, we included 15 studies for review and quantitatively synthesised data from 184 dams and 323 offspring in rat models.

Results indicate maternal sucrose consumption prior to conception and during prenatal periods did not affect maternal BW. However, a significant increase in the BW of the adult offspring was identified. A sex effect was not evident in sub-group analyses, although this conclusion was limited by a paucity of female data. Sex differences have been reported in developmental programming, although they are not commonly explored.[50,51] Literature suggests that male offspring may be more susceptible to programming of adiposity and BW than females, with the protective actions of oestrogen, maternal and paternal epigenetics and sex disparities in placental function possible mechanisms.[50-53] It is clear future studies must include female and male offspring to elucidate if sexual dimorphism exist.

A more accurate assessment of offspring adiposity can be obtained from changes in body composition rather than simple BW measurements. The latter may not indicate the contribution of prenatal food manipulation to abdominal fat.[54] Toop *et al.*[30] reported lower retroperitoneal adipose tissue in female adult offspring exposed to sucrose during pregnancy and lower relative total fat and visceral fat mass in adult males exposed during lactation. This was despite having similar BW to control offspring. This decrease in fat mass contrasts to the findings of Kisoglu *et al.*[38] who reported higher total body fat assessed by Soxhlet extraction, along with increased BW in 3-week-old pups, although sex was not considered in these data. In general, differing results limit our ability to

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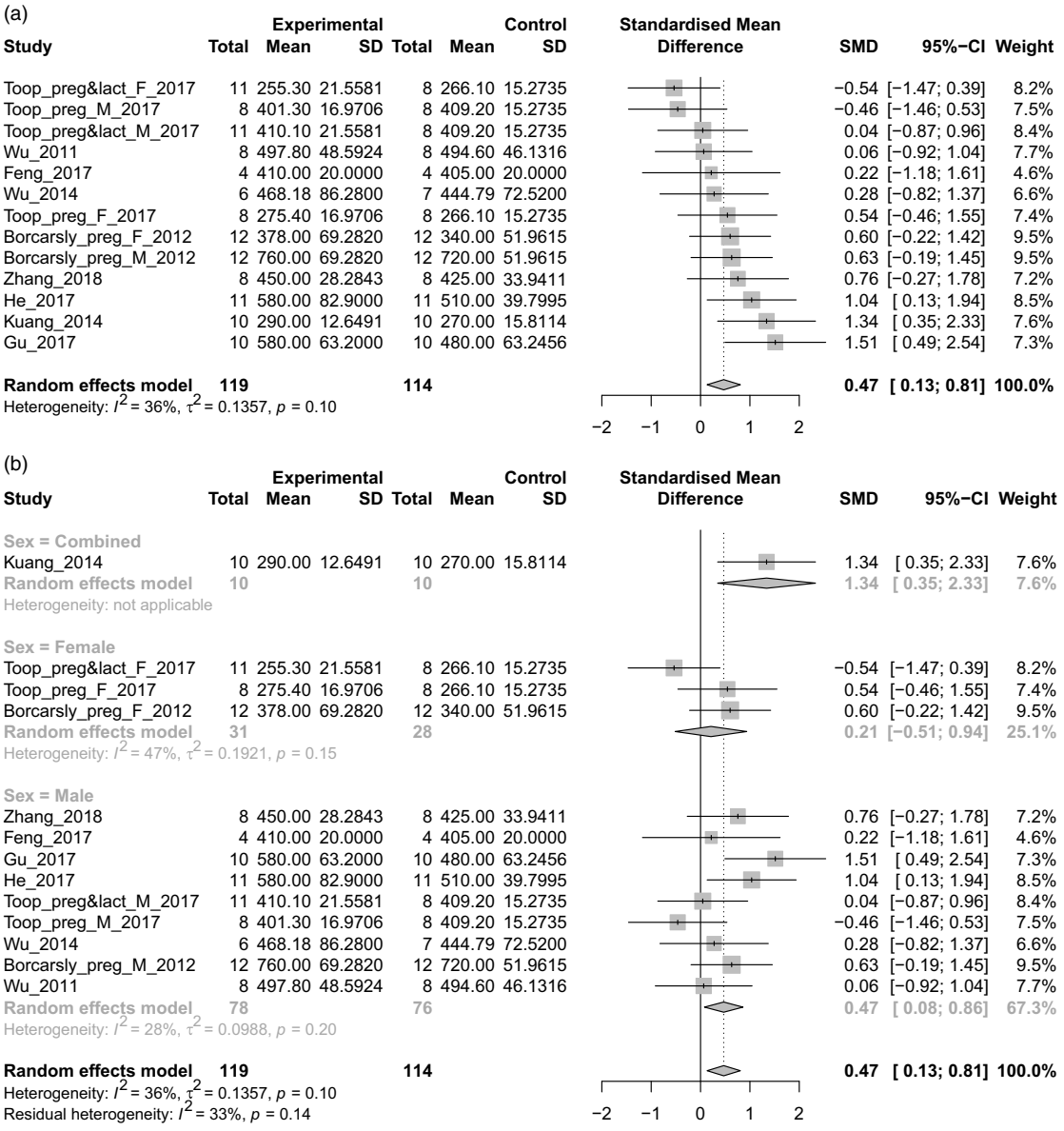

Fig. 5. (a) Offspring body weight adult. (b) Offspring body weight adult sex. (c) Offspring body weight adult concentration. (d) Offspring body weight adult strain. (e) Offspring body weight adult exposure.

interpret the potential influences prenatal sucrose exposure may have on offspring adiposity.

Hyperglycaemia and reduced glucose tolerance were evident in dams, particularly at the higher concentration of 20% w/v; however, meta-analyses did not reveal a change in the FGLs of adult offspring. When analysing outcomes for glycaemic control, we identified a number of different measures utilised, including GTT and indices from static assessment of glucose and insulin levels, such as QUICKI and HOMA-IR estimates. These were measured at varied ages in offspring. In the pre-weaning period and early adulthood, no effect was shown in male or females during OGTT[48] or intraperitoneal GTT[30,40] or in a study with combined sexes using HOMA-IR and QUICKI estimates.[43] It was only when assessing older male rats, from 4 to 18 months in age, that reduced glucose tolerance was observed with[42] and without[39] hyperinsulinaemia. Of note, Zhang *et al.*[39] found this effect was normalised when the 4-month-old offspring were re-assessed at 6 months and their data show the transient nature of glycaemic homoeostasis. Overall, results suggest that prenatal sucrose exposure did not impact the FGLs or glycaemic control in younger offspring, and it was not until rats aged that poor glucose disposal became evident. However, in many cases, prenatal exposure was confounded with an altered maternal metabolic state at the outset of pregnancy.

At the outset of this review, we included secondary behavioural outcomes for food and fluid intakes and sweet taste preferences to determine if maternal sucrose consumption elicits hyperphagia or modulate taste preferences in offspring. While consumption was

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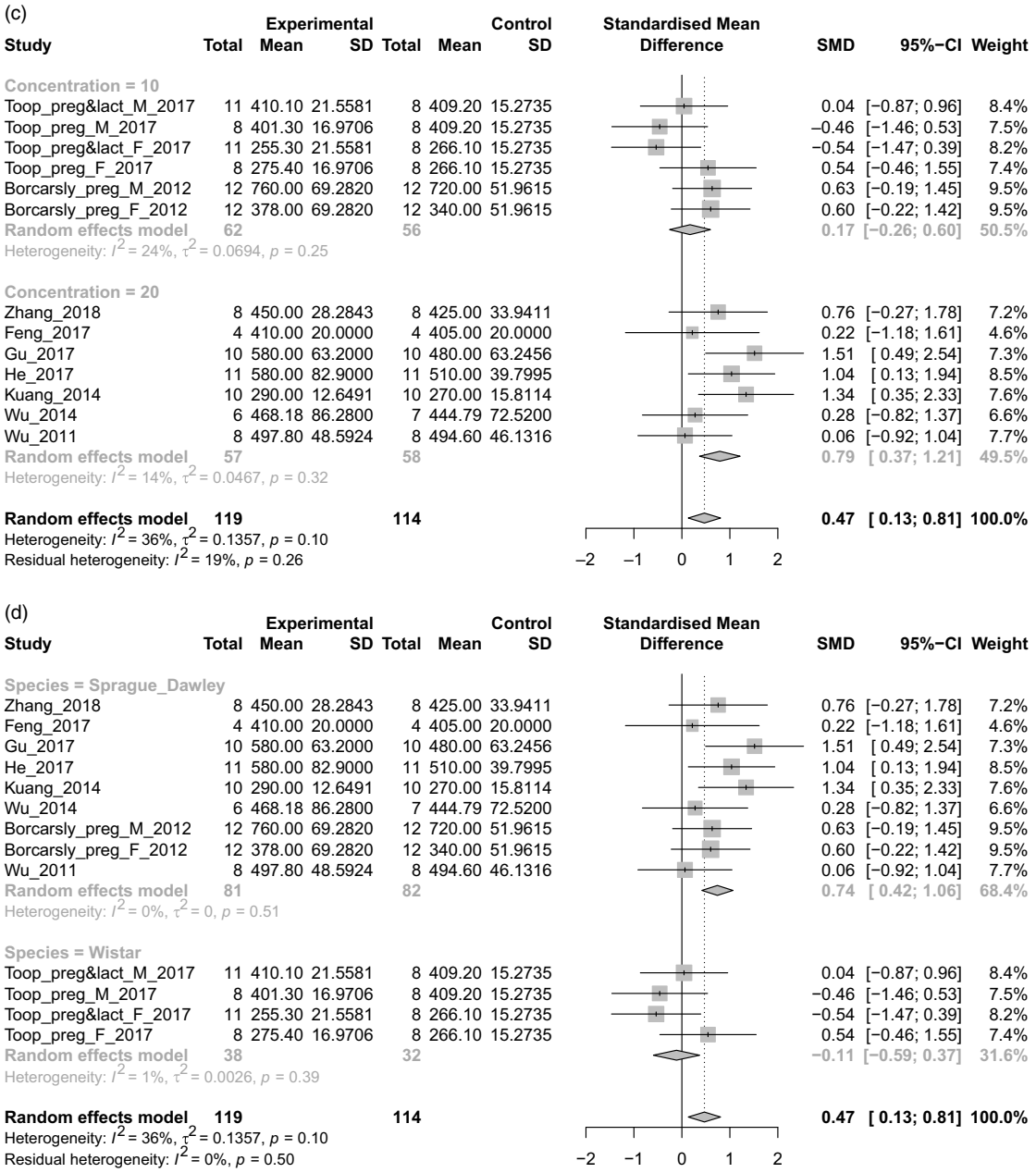

Fig. 5. *(Continued)*.

not frequently reported, studies that did report such data found no effect on offspring intakes.[30,39,42,48] No study investigating sweet preference in offspring at relevant sucrose concentrations was identified.

Cross-fostering is a valuable research tool for providing insights into the effects of sucrose exposure during crucial time-periods, i.e. lactation or pregnancy.[55] Two studies utilised this approach and both found that offspring effects were dependent on the exposure window.[30,31] Some over-nutrition models suggest lactation to be a critical time-point, displaying developmental programming of obesity.[13,56,57] Bocarsly *et al.* results support this suggestion, finding adult males were heavier in the lactation group compared to control and pregnancy groups.[31] Although Toop *et al.* observed no change to BW, exposure during the lactation period had a greater impact on adipose tissue deposition. When animals were exposed during pregnancy and lactation, poorer metabolic fatty acid profiles were also evident.[30] Notwithstanding differences between the development of human and rodent models, these results suggest health recommendations should highlight the importance of reducing SSB consumption not only during pregnancy but also throughout the lactation period.

The current review allows for exploration of mechanisms between maternal sucrose consumption and developmental programming of offspring. Some studies suggest the dysregulation of insulin signalling pathways and lipogenesis may play a role in programming offspring phenotypes.[29,30,39,43] Zhang *et al.* reported

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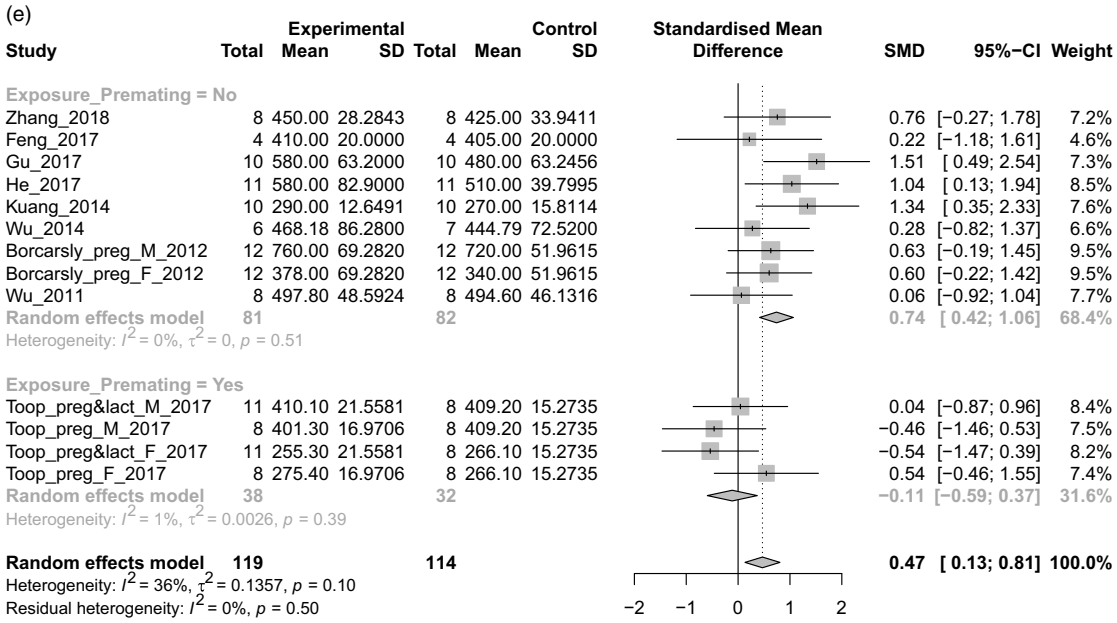

Fig. 5. *(Continued).*

a downregulation of mRNA expression of key hepatic insulin signalling molecules IRS-1, Akt and GSK-3β, although protein expression remained unchanged.[39] Adult offspring also displayed reduced glucose tolerance and enlarged pancreatic islets. Supporting these results, Ozkan *et al.* observed damage to offspring pancreatic tissue, with pups showing decreased insulin secretion and insulin receptor expression, worsening with higher sucrose concentrations.[43] Altered adipocyte programming was suggested for changes to adipose deposits in offspring with concomitant elevation of plasma free fatty acids (FFA) concentration and hepatic lipid content.[30] Yuruk *et al.* also found maternal sucrose consumption had a significant effect on increasing hepatic and liver TG and circulating NEFA levels at weaning. Other mechanisms in programming of obesity were explored, including altered appetite regulation[38] and sensitisation of reward pathways.[31] Kisogulu *et al.* found elevated offspring BWs were associated with dysregulation of satiety peptides leptin and ghrelin, although free fructose appeared to have a more significant effect than sucrose.[38] Of note, this study did not report offspring food intake. From the limited data on offspring food or fluid intake, no effect from maternal sucrose consumption was seen.[30,39,42,48] Taken together, a possible interplay of programming in metabolic pathways and appetite regulation may have detrimental effects on offspring phenotypes in rat models. Whether these mechanisms differ between rat and human systems remain unclear.

A fundamental reason for performing animal studies is to translate the outcomes to human health. There are calls amongst the academic community that rodent experimentation should more closely mimic the dietary and feeding behaviours of humans,[58] although some studies do not adhere to this principle. In our recent systematic review investigating metabolic and behavioural effects of prenatal exposure to non-nutritive sweeteners (NNS), we found many studies provided animals with NNS dosages that were not physiologically relevant to human consumption, hampering translational capacity.[37] The current review builds upon this research by only including sucrose concentrations found in commercially available SSBs. Nevertheless, it is important to acknowledge other factors can limit rodent-to-human translation when investigating maternal high-sugar diets. For example, overdrinking of sucrose solution with a compensatory reduction in chow intake was
commonly observed in dams.[48,49] In this case, it is possible that the observed offspring effects may be impacted by maternal protein restriction rather than, or in addition, to the excess sugar. Protein undernutrition appears to be important in the programming of metabolic disorders.[59] Given the majority of pregnant women exceed the minimum recommendations for protein intake,[60] one must question whether this rodent model adequately reflects human consumption patterns.

While the effects identified in this review are not as pronounced as those reported for offspring exposed during prenatal life to high-fat/high-sugar diets,[12,13,20] it is apparent the isolated effects of sucrose may contribute to metabolic developmental programming. Thus, recommendations to reduce intake of SSBs prior to conception and during pregnancy remain valid.

Strengths and limitations

Common practice in research of developmental programming is to target outcomes in males only.[12,15,32] This is evident in our review; over two-thirds of the offspring investigated were male. A number of studies reported results for both sexes combined together.[29,43] Sexual dimorphism has frequently been observed for both human and animal metabolic programming;[61,62] however, limited data meant that no firm conclusions could be reached on sex-specific differences. Future studies should include both males and females

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Table 3. Summary of offspring glycaemic outcome measures. Reported outcomes extracted include offspring fasting plasma or blood glucose levels, fasting plasma insulin levels and other assessments for glycaemic control

						Summary of Offspring Glycaemic Measures: Effect of Sucrose Exposure Relative to Control			
Citation	Rat Strain	Sucrose Concentration (% w/v)	Sucrose Exposure	N	FGL	FPI	Method	Glycaemic Measure	Age Measured
Ozkan (2019)	– –	10 20	G, L G, L	14 14	Significant ↑ (mixed sex) Significant ↑ (mixed sex)	Significant ↑ (mixed sex) Significant ↑ (mixed sex)	– –	– –	PND28 PND28
Zhang (2018)	SD	20	G only	7 - 9♂	No effect ♂	No effect ♂	IPGTT HOMA-IR	Significant ↑♂ at 30 min time-point (PND112) No effect ♂ (PND168) No effect ♂	PND112 PND168 PND112
Feng (2017)	SD	20	G only	8–12 ♂	Significant ↑♂	–	–	–	PND112
Gu (2017)	SD	20	G only	10 ♂	Significant ↑♂	–	–	–	PND140
He (2017)	SD	20	G only	8 ♂	No effect ♂	Significant ↑♂	IPGTT HOMA-IR	Significant ↑♂ at 30 min time-point Significant ↑♂	PND504
Toop (2017)	WS	10	4 weeks PC, G, and/or L∞	5–11 ♂ 5–11 ♀ 5–11 ♂ 5–11 ♀	Significant ↓ ♂[f] Significant ↓ ♀[c] No effect ♂[d,e,f] No effect ♀[a,b,c]	No effect ♂ [d,e,f] No effect ♀ [a,b,c] No effect ♂ [d,e,f] No effect ♀ [a,b,c]	IPGTT IPGTT	No effect ♂ [d,e,f] No effect ♀ [a,b,c] No effect ♂ [d,e,f] No effect ♀ [a,b,c]	PND21 PND84
Yuruk (2017)	SD	20	12 weeks PC, P, L	6–7	No effect (mixed sex)	No effect (mixed sex)	HOMA-IR QUICKI	No effect (mixed sex) No effect (mixed sex)	PND21
Wu (2016)	SD	20	G only	6 ♂	No effect ♂	–	–	–	PND616
Kendig (2014)	WS	10	4 weeks PC, P, L Male offspring fed sucrose PND91142	7 ♂ 7 ♀ 10 ♂	No effect ♂ No effect ♀ Significant ↑ ♂†		OGTT QUICKI	No effect ♂ No effect ♀ ↓ Insulin sensitivity ♂†	PNDP89–94 PND142
Toop (2015)	WS	10	4 weeks PC, P, L	6 ♂ 5 ♀	No effect ♂, ♀	No effect ♂, ♀	–	–	PND1
Wu (2014)	SD	20	G only	8	No effect ♂	–	–	–	PND140
Wu (2011)	SD	20	G only		No effect ♂	–	–	–	PND140

FGL – fasting glucose level; FPI – fasting plasma insulin; G – gestation; IPGTT – intraperitoneal glucose tolerance test; N – sample size; NR – not reported; OGTT – oral glucose tolerance test; PND – postnatal day; PC – pre-conception; PND – postnatal day; SD – Sprague-Dawley; WS – Wistar; % w/v – concentration percentage weight per volume; – outcome not measured; ↑ – increase; ↓ – decrease; ♂ - male; ♀ - female.
[a]In female interventional group exposed to sucrose during gestation period only (cross-fostering model).
[b]In female interventional group exposed to sucrose during lactation period only (cross-fostering model).
[c]In female interventional group exposed to sucrose during gestation and lactation periods (cross-fostering model).
[d]In male interventional group exposed to sucrose during gestation period only (cross-fostering model).
[e]In male interventional group exposed to sucrose during lactation period only (cross-fostering model).
[f]In male interventional group exposed to sucrose during gestation and lactation (cross-fostering model).
† In male interventional group when sucrose was added to their diet from PND91 to 142 compared to control offspring.
∞ Cross-fostering model.

in their study design, with analyses exploring sex effect and sex by treatment interactions.

A comprehensive assessment of the study and reporting quality identified a high risk of bias and low or moderate adherence of reporting guidelines for many of the included studies. Generally, studies lacked appropriate reporting on randomisation and blinding techniques. This drawback has the potential to affect the internal bias of a study and may promote overestimation of the effects of the intervention.[63] A further concern, relevant to rodents having multiparous births, is the effect of litter on statistical analysis. For conclusions to be valid, each dam and its litter should be considered one experimental unit. If individual offspring are counted as its own experimental unit, this gives rise to an increase in Type 1 errors.[13,64] In over two-thirds of the studies, the experimental unit was not made clear. As such, we could not determine if statistical analyses in these studies used inflated sample sizes, which may lead to false-positive results.

The strengths of this review include detailed assessment of the quality of the studies it covers and meta-analyses, with sub-group analyses to explore heterogeneity in study design. Importantly, this

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Table 4. Summary of risk of bias assessment according to SYRCLE's tool (Hooijmans et al., 2014). Results are presented for individual papers with questions judged as 'low' risk of bias, 'high' risk of bias or 'unclear' if unable to clearly assign risk, according to pre-defined signalling questions (hoojimans). Five types of bias and assessment of litter as a unit of analysis are included for assessment

	Question and Bias Type									
Citation	Q1 Selection	Q2 Selection	Q3 Selection	Q4 Performance	Q5 Performance	Q6 Detection	Q7 Detection	Q8 Attrition	Q9 Reporting	Q10 Litter as a Unit of Analysis
Ozkan (2019)	Unclear	High	High	Unclear	Unclear	Unclear	Low	Low	Low	High
Kisioglu (2018)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
Zhang (2018)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Feng (2017)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear
Gu (2017)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear
He (2017)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
Toop (2017)	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
Yuruk (2017)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Wu (2016)	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Unclear
Kendig (2015)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Low
Toop (2015)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
Kuang (2014)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Wu (2014)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Bocarsley (2012)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Wu (2011)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low	Unclear

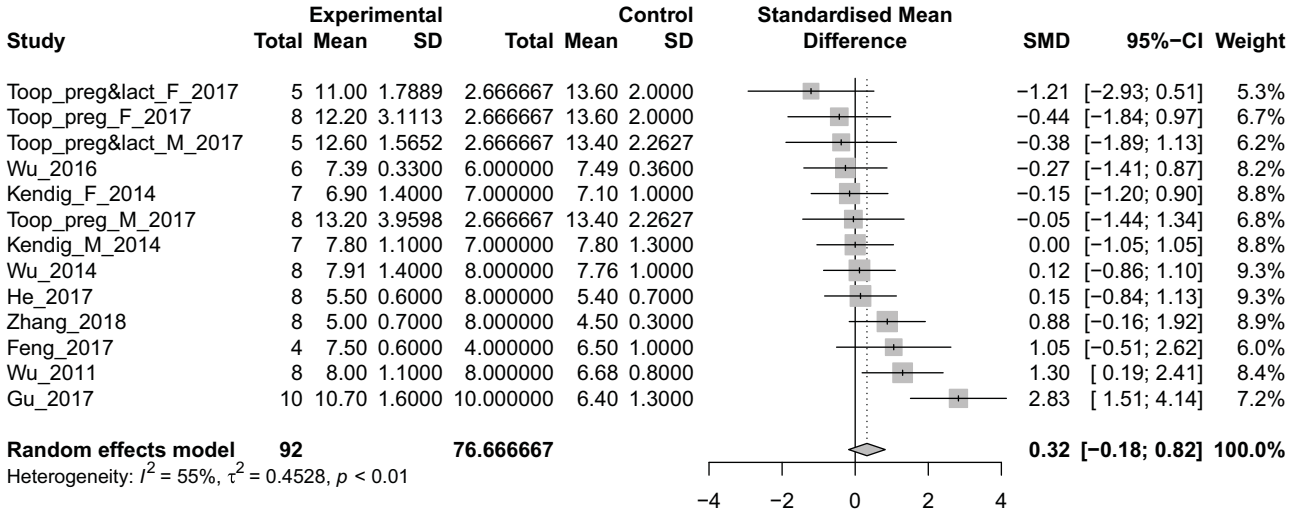

Fig. 6. Offspring BGL adult.

review offers insights for translational relevance by including sucrose concentrations that mimic aspects of the human diet when consuming SSBs.

Conclusion

Sucrose consumption prior to conception or during pregnancy, at concentrations similar to that of SSBs, elicits hyperglycaemia and adiposity with no change to bodyweight in dams. A paucity of female offspring data limited our capacity to identify potential sexually dimorphic responses in body composition and glycaemic control; therefore, future studies must include both sexes. We also revealed study design and reporting weaknesses, predisposing many of the papers to bias. Although our data did not mirror results from epidemiological studies for significant risks of childhood obesity, our review identified a risk of obesity and poor glucose control in adult offspring. These effects were not as pronounced as those obtained from research using maternal high-fat/high-sugar diets. Current recommendations to reduce consumption of SSBs during pregnancy and lactation remain

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valid, not only for the metabolic health of mothers but also for that of future generations.

Supplementary mterial. For supplementary material for this article, please visit https://doi.org/10.1017/S2040174420000823

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Conflicts of interest. None.

Ethical standards. The authors assert this research was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement.

References

1. Ng M, Fleming T, Robinson M, *et al.* 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. *Lancet.* 2013; 384, 766–81.
2. World Health Organisation. Obesity and overweight fact sheet. https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. 2016.
3. Bailey R, Fulgoni V, Cowan A, Gaine P. Sources of added sugars in young children, adolescents, and adults with low and high intakes of added sugars. *Nutrition.* 2018; 10, 102.
4. Luger M, Lafontan M, Bes-Rastrollo M, Winzer E, Yumuk V, Farpour-Lambert N sugar-sweetened beverages and weight gain in children and adults: a systematic review from 2013 to 2015 and a comparison with previous studies. *Obes Facts.* 2017; 10, 674–693.
5. Qi Q, Chu AY, Kang JH, *et al.* Sugar-sweetened beverages and genetic risk of obesity. *New Engl J Med.* 2012; 367, 1387–1396. https://doi.org/10.1056/NEJMoa1203039
6. Malik VS, Hu FB. Sweeteners and risk of obesity and type 2 diabetes: the role of sugar-sweetened beverages. *Curr Diabetes Rep.* 2012; 12, 195–203. https://doi.org/10.1007/s11892-012-0259-6
7. Te Morenga L, Mallard S, Mann J. (2012). Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ.* 2012; 346, e7492
8. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Internal Med.* 2014; 174, 516.
9. Whitaker RC. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. *Pediatrics.* 2004; 114, e29–e36.
10. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. *BMJ.* 2017; 356, j1. doi: 10.1136/bmj.j1.
11. Parlee SD, MacDougald OA. Maternal nutrition and risk of obesity in offspring: the Trojan horse of developmental plasticity. *Biochim Biophys Acta.* 2014; 1842, 495–506.
12. Ainge H, Thompson C, Ozanne SE, Rooney KB. A systematic review on animal models of maternal high fat feeding and offspring glycaemic control. *Int J Obes.* 2011; 35, 325–335. doi: 10.1038/ijo.2010.149.
13. Ribaroff GA, Wastnedge E, Drake AJ, Sharpe RM, Chambers TJG. Animal models of maternal high fat diet exposure and effects on metabolism in offspring: a meta-regression analysis: maternal HFD and offspring metabolism. *Obes Rev.* 2017; 18, 673–686.
14. Camilleri-Carter TL, Dowling DK, Robker RL, Piper MDW. Transgenerational obesity and healthy aging in drosophila. *J Gerontol: Ser A.* 2019; 74, 1582–89. https://doi.org/10.1093/gerona/glz154.
15. Desai M, Beall M, Ross MG. Developmental origins of obesity: programmed adipogenesis. *Curr Diabetes Rep.* 2013; 13, 27–33. https://doi.org/10.1007/s11892-012-0344-x
16. Fernandez-Twinn DS, Constância M, Ozanne SE. (2015). Intergenerational epigenetic inheritance in models of developmental programming of adult disease. *Semin Cell Dev Biol.* 2015; 43, 85–95. https://doi.org/10.1016/j.semcdb.2015.06.006
17. Gillman MW, Rifas-Shiman SL, Fernandez-Barres S, Kleinman K, Taveras EM, Oken E. Beverage intake during pregnancy and childhood adiposity. *Pediatrics*, 2017; 140, e20170031. https://doi.org/10.1542/peds.2017-0031
18. Jen V, Erler NS, Tielemans MJ, *et al.* Mothers' intake of sugar-containing beverages during pregnancy and body composition of their children during childhood: the Generation R Study. *Am J Clin Nutr.* 2017; 105, 834–841. https://doi.org/10.3945/ajcn.116.147934
19. Chen L-W, Aris IM, Bernard JY, *et al.* Associations of maternal macronutrient intake during pregnancy with infant BMI peak characteristics and childhood BMI. *Am J Clin Nutr.* 2017; 1053, 705–713. https://doi.org/10.3945/ajcn.116.148270
20. Tellechea ML, Mensegue MF, Pirola CJ. The association between high fat diet around gestation and metabolic syndrome-related phenotypes in rats: a systematic review and meta-analysis. *Sci Rep.* 2017; 7, 5086.
21. Christians JK, Lennie KI, Wild LK, Garcha R. Effects of high-fat diets on fetal growth in rodents: a systematic review. *Reprod Biol Endocrinol.* 2019; 17, 39.
22. Vickers MH, Clayton ZE, Yap C, Sloboda DM. Maternal fructose intake during pregnancy and lactation alters placental growth and leads to sex-specific changes in fetal and neonatal endocrine function. *Endocrinology.* 2011; 152, 1378–1387.
23. D'Alessandro ME, Oliva ME, Fortino MA, Chicco A Maternal sucrose-rich diet and fetal programming: changes in hepatic lipogenic and oxidative enzymes and glucose homeostasis in adult offspring. *Food Funct.* 2014; 5, 446. https://doi.org/10.1039/c3fo60436e
24. Samuelsson A-M, Matthews PA, Jansen E, Taylor PD, Poston L. Sucrose feeding in mouse pregnancy leads to hypertension, and sex-linked obesity and insulin resistance in female offspring. *FrontPhysiol.* 2013; 4, 14. https://doi.org/10.3389/fphys.2013.00014
25. D'Alessandro ME, Oliva ME, Ferreira MR, Selenscig D, Lombardo YB, Chicco A. Sucrose-rich feeding during rat pregnancy-lactation and/or after weaning alters glucose and lipid metabolism in adult offspring. *Clin Exp Pharmacol Physiol.* 2012; 39, 623–629. https://doi.org/10.1111/j.1440-1681.2012.05720.x
26. de Vries RBM, Hooijmans CR, Langendam MW, *et al.* A protocol format for the preparation, registration and publication of systematic reviews of animal intervention studies: protocol format for animal systematic reviews. *Evidence-Based Preclin Med.* 2015; 2, e00007. https://doi.org/10.1002/ebm2.7
27. Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. *Lab Anim.* 2010; 44, 170–175. https://doi.org/10.1258/la.2010.009117
28. de Vries RBM, Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. Letter to the editor. *Lab Anim.* 2014; 48, 88–88
29. Ozkan H Topsakal S, Ozmen O. Investigation of the diabetic effects of maternal high-glucose diet on rats. *Biomed Pharmacother.* 2019; 110, 609–617.
30. Toop CR, Muhlhausler BS, O'Dea K., Gentili S. Impact of perinatal exposure to sucrose or high fructose corn syrup (HFCS-55) on adiposity and hepatic lipid composition in rat offspring: perinatal exposure to sucrose or HFCS-55. *J Physiol.*2017; 595, 4379–4398.
31. Bocarsly ME Barson JR, Hauca JM, *et al.* Effects of perinatal exposure to palatable diets on body weight and sensitivity to drugs of abuse in rats. *Physiol Behav.* 2012; 107, 568–575.
32. Vesterinen HM, Sena ES, Egan KJ, *et al.* Meta-analysis of data from animal studies: a practical guide. *J Neurosci Methods.* 2014; 221, 92–102. https://doi.org/10.1016/j.jneumeth.2013.09.010.
33. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M. Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol.* 2014; 14, 43. https://doi.org/10.1186/1471-2288-14-43.
34. Higgins JPT, Altman DG, Gotzsche PC, *et al.* The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011; 343, d5928–d5928. https://doi.org/10.1136/bmj.d5928.

35. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol.* 2010; 8, e1000412. https://doi.org/10.1371/journal.pbio.1000412.
36. IICARus training resource, https://ecrf1.clinicaltrials.ed.ac.uk/iicarus/IICARusResource.pdf. Accessed 8th March 2019.
37. Morahan HL, Leenaars CHC, Boakes RA, Rooney KB. Metabolic and behavioural effects of prenatal exposure to non-nutritive sweeteners: a systematic review and meta-analysis of rodent models. *Physiol Behav.* 2020; 213, 112696.
38. Kisioglu B, Nergiz-Unal R. Potential effect of maternal dietary sucrose or fructose syrup on CD36, leptin, and ghrelin-mediated fetal programming of obesity. *Nutr Neurosci.*, 2018; 23, 210–220. doi: 10.1080/1028415X.2018.1491151.
39. Zhang P, Zhu D, Zhang Y, *et al.* Synergetic effects of prenatal and postnatal high sucrose intake on glucose tolerance and hepatic insulin resistance in rat offspring. *Mol Nutr Food Res.* 2018; 62, 1700771.
40. Feng X, Zhou X, Zhang W, *et al.* Maternal high-sucrose diets altered vascular large-conductance $Ca2^{+}$-activated K+ channels via reactive oxygen species in offspring rats†. *Biol Reprod.* 2017; 96, 1085–1095.
41. Gu X, He A, Fan X, *et al.* Regulation of cerebral arterial BKCa channels by angiotensin II signaling in adult offspring exposed to prenatal high sucrose diets. *Biosci Rep.* 2017; 37, BSR20160624.
42. He A, Zhang Y, Yang Y, *et al.* Prenatal high sucrose intake affected learning and memory of aged rat offspring with abnormal oxidative stress and NMDARs/Wnt signaling in the hippocampus. *Brain Res.* 1669, 2017; 114–121.
43. Yuruk AA, Nergiz-Unal R. Maternal dietary free or bound fructose diversely influence developmental programming of lipogenesis. *Lipids Health Dis.* 2017; 16, 226.
44. Wu L, Shi A, Zhu D, *et al.* High sucrose intake during gestation increases angiotensin II type 1 receptor-mediated vascular contractility associated with epigenetic alterations in aged offspring rats. *Peptides.* 2016; 86, 133–144.
45. Kuang H, Sun M, Lv J, *et al.* Hippocampal apoptosis involved in learning deficits in the offspring exposed to maternal high sucrose diets. *J Nutr Biochem.* 2014; 25, 985–990.
46. Wu C, Li J, Bo L, *et al.* High-sucrose diets in pregnancy alter angiotensin II-mediated pressor response and microvessel tone via the PKC/Cav1.2 pathway in rat offspring. *Hypertens Res.* 2014; 37, 818–823.
47. Wu L, Mao C, Liu Y, *et al.* Altered dipsogenic responses and expression of angiotensin receptors in the offspring exposed to prenatal high sucrose. *Peptides.* 2011; 32, 104–111.
48. Kendig MD, Ekayanti W, Stewart H, Boakes RA, Rooney K. Metabolic effects of access to sucrose drink in female rats and transmission of some effects to their offspring. *PLoS ONE.* 2015; 10, e0131107.
49. Toop CR, Muhlhausler BS, O'Dea K, Gentili S. Consumption of sucrose, but not high fructose corn syrup, leads to increased adiposity and dyslipidaemia in the pregnant and lactating rat. *J Dev Orig Health Dis.* 2015; 6, 38–46.
50. Dearden L, Bouret SG, Ozanne SE. Sex and gender differences in developmental programming of metabolism. *Mol Metabo.*2018; 15, 8–19.
51. Aiken CE, Ozanne SE. Sex differences in developmental programming models. *Reproduction.* 2013; 145, R1–R13.
52. Shi H, Strader AD, Sorrel JE, Chambers JB, Woods SC, Seeley RJ. Sexually different actions of leptin in proopiomelanocortin neurons to regulate glucose homeostasis. *Am J Physiol-Endocrinol Metab.* 2008; 294, E630–E639.
53. Li J, Tsuprykov O, Yang X, Hocher B. Paternal programming of offspring cardiometabolic diseases in later life. *J Hypertens.* 2016; 34, 2111–2126.
54. Eleftheriades M, Vafaei H, Dontas I, *et al.* Assessment of body composition in Wistar rat offspring by DXA in relation to prenatal and postnatal nutritional manipulation. *Pediatr Res.* 2016; 80, 319.
55. Dickinson H, Moss T, Gatford K, *et al.* A review of fundamental principles for animal models of DOHaD research: an Australian perspective. *J Dev Orig Health Dis.* 2016; 7, 449–472.
56. Lagisz M, Blair H, Kenyon P, *et al.* Little appetite for obesity: meta-analysis of the effects of maternal obesogenic diets on offspring food intake and body mass in rodents. *Int J Obes.* 2015; 39, 1669–1678.
57. Alfaradhi MZ, Ozanne SE. Developmental programming in response to maternal Overnutrition. *Front Gene.* 2011; 2, 27.
58. Speakman JR. Use of high-fat diets to study rodent obesity as a model of human obesity. *Int J Obes.* 2019; 43, 1491–1492.
59. Fernandez-Twinn DS, Wayman A, Ekizoglou S, *et al.* Maternal protein restriction leads to hyperinsulinemia and reduced insulin-signaling protein expression in 21-mo-old female rat offspring. *Am J Physiol-Regul Integr Comp Physiol.* 2005; 288, R368–R373.
60. Australian Bureau of Statistics: Australian Health Survey: Usual Nutrient Intakes, 2011-12; https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.008~2011-12~Main%20Features~Macronutrients~200. Published 2015.
61. Ravelli AC, van der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr.* 1999; 70, 811–816.
62. Fuente-Martín E, Granado M, Garcia-Caceres C, *et al.* vsd. *Metabolism.* 2012; 61, 812–822.
63. Macleod MR, van der Worp HB, Sena ES, Howells DW, Dirnagl U, Donnan GA. Evidence for the efficacy of NXY-059 in experimental focal cerebral ischaemia is confounded by study quality. *Stroke.* 2008; 39, 2824–2829.
64. Lazic SE, Essioux L. Improving basic and translational science by accounting for litter-to-litter variation in animal models. *BMC Neurosci.* 2013; 14, 37.