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REVIEW

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The capacity for oestrogen to influence obesity through brown adipose tissue thermogenesis in animal models: A systematic review and meta-analysis

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Summary

Pharmacological interventions to aid weight loss have historically targeted either appetite suppression or increased metabolic rate. Brown adipose tissue (BAT) possesses the capacity to expend energy in a futile cycle, thus increasing basal metabolic rate. In animal models, oestrogen has been implicated in the regulation of body weight, and it is hypothesized that oestrogen is acting by modulating BAT metabolism. A systematic search was performed, to identify research articles implementing in vivo oestrogen-related interventions and reporting outcome measures that provide direct or indirect measures of BAT metabolism. Meta-analyses were conducted where sufficient data were available. The final library of 67 articles were predominantly in rodent models and provided mostly indirect measures of BAT metabolism. Results of this review found that oestrogen's effects on body weight, in rats and possibly mice, are likely facilitated by both metabolic and appetitive mechanisms but are largely only found in ovariectomized models. There is a need for further studies to clarify the potential effects of oestrogen on BAT metabolism in gonad-intact and castrated male animal models.

KEYWORDS

Animal models, brown adipose tissue, oestrogen, thermogenesis

1 | INTRODUCTION

The pathogenesis of obesity can be largely explained by an imbalance between caloric intake and caloric outflow,[1] but the underlying mechanisms are far more complex. Among the contributing factors that remain unresolved are the influence of metabolic rate, physiological perception of satiety, and neurohormonal control of feeding behaviour.[1] The focus of this review is on one of these influencing factors, metabolic rate, and how it is modulated by brown adipose tissue (BAT) activity. A paucity of BAT in adult humans has been correlated to development of obesity in later life.[2] During typical physiological activity, BAT uses energy to produce heat (rather than ATP), as part of thermoregulatory cold-defence.[3] BAT is also exploited by the body to increase energy expenditure after a meal, even if temperatures are above the thermoneutral zone, as part of the physiological response known as

ABBREVIATIONS: AR, adrenergic receptor; BAT, brown adipose tissue; BPA, bisphenol A; GLP1, glucagon-like protein 1; GPER, G protein-coupled oestrogen receptor; NR3A1, oestrogen receptor alpha; NR3A2, oestrogen receptor beta; OVX, ovariectomized; RER, respiratory exchange ratio; UCP1, uncoupling protein 1; VMH, ventromedial hypothalamus.

diet-induced thermogenesis.[4] Additionally, increased BAT activity increases insulin sensitivity (improving glucostasis) [5] and stimulates BAT cell proliferation.[4] Therefore, therapies that increase BAT activity in humans could (a) increase metabolism—potentially leading to weight loss, (b) improve glucose tolerance—decreasing risk of diabetes mellitus type II, and (c) increase BAT mass—creating a positive cycle that will ultimately reduce obesity and metabolic syndrome comorbidities. With these observations in mind, it would seem desirable to target and activate BAT and exploit it as an anti-obesity therapy.

There exist some experimental interventions that, in rodents, stimulate or restore BAT activity.[6] Experiments have implicated oestrogen as a key modulator of BAT activity.[7] Female rats seemingly gain weight when endogenous oestrogen is removed (by ovariectomy), and subsequent weight gain is attenuated upon the administration of exogenous oestrogen.[7] Ovariectomy is a commonly used, experimental, animal model for investigating postmenopausal weight gain. Given oestrogen's capacity to attenuate weight gain in this animal model, it is therefore promising in its application to humans. Postovariectomy weight gain can be alleviated in animals, by administering exogenous oestrogen either peripherally via intravenous (IV) injection or to the central nervous system (CNS) via intracerebroventricular (ICV) injection.[7] Additionally, weight gain, similar to that observed following ovariectomy, can be reproduced by oestrogen receptor knockout (ER-KO). Knockout of either the nuclear receptor oestrogen receptor alpha (NR3A1), or the G protein-coupled oestrogen receptor (GPER), elicits weight gain.[8]

Thus, the research question is whether decreased oestrogen levels will reduce BAT thermogenesis (Figure 1). Measures used to quantify BAT thermogenesis include uncoupling protein 1 (UCP1) expression, sympathetic discharge to BAT, and BAT responsiveness to norepinephrine.[7,9] These outcome measures are of interest because UCP1 facilitates thermogenesis in BAT by uncoupling the proton gradient in mitochondria, sympathetic discharge to BAT releases norepinephrine thereby stimulating thermogenesis, and the sensitivity of BAT to norepinephrine influences the efficacy of sympathetic discharge to BAT. Decreased BAT thermogenesis could also be less directly inferred from outcome measures such as decreased oxygen consumption/decreased energy expenditure (because BAT thermogenesis contributes to oxygen consumption and energy expenditure by the futile cycle), increased body weight (as changes in energy expenditure can manifest as changes in body weight), or increased respiratory exchange ratio (RER). Because the primary substrate of BAT is free fatty acids, this may be reflected in the RER.

While the effect of oestrogen on metabolism, mostly in female rodents, has been the subject of a number of experimental papers[7,10,11] and narrative reviews,[12-14] a systematic review and/or meta-analysis has never been conducted. The purpose of this systematic review and meta-analysis is to definitively characterize the effect of oestrogen on metabolism in animal models and to compare any potential differences between genders and species.

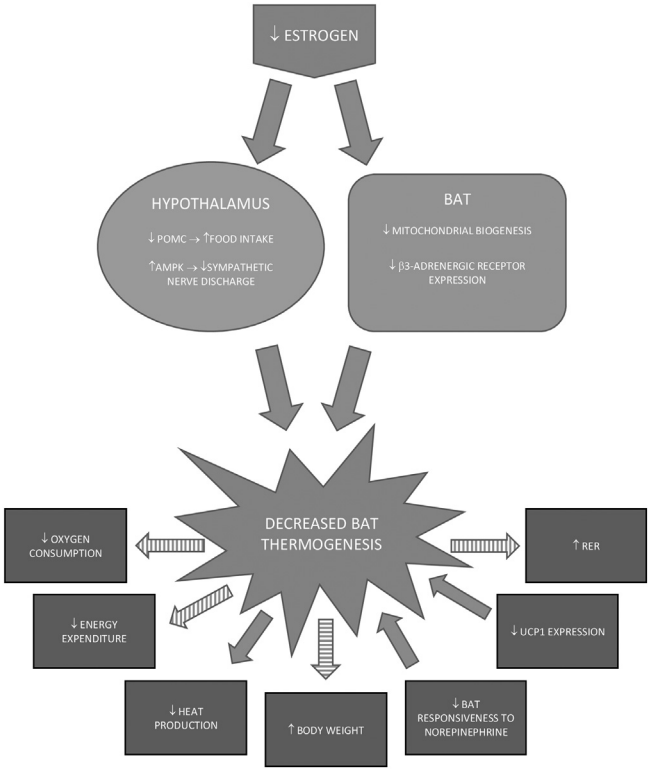

FIGURE 1 A flow chart illustrating proposed physiological responses to removal of endogenous oestrogen. From top to bottom: It is proposed that decreased oestrogen levels cause changes in both the hypothalamus and BAT. Hypothalamic levels of POMC decrease, leading to an increase in food intake, while increased hypothalamic AMPK causes increase sympathetic activity. In parallel to hypothalamic changes, mitochondrial biogenesis and β3-AR expression are decreased in BAT. These parallel changes in BAT and the hypothalamus both contribute to decreased BAT thermogenesis. Outcome measures used experimentally to infer decreased BAT thermogenesis are shown radially around the "decreased BAT thermogenesis" bubble. Solid arrows indicate outcome measures more directly linked with BAT thermogenesis, while striped arrows represent intermediate steps, and thus a more indirect relationship. Direction of arrows infers direction of causality. AMPK, adenosine monophosphate-activated protein kinase; BAT, brown adipose tissue; POMC, pro-opiomelanocortin; RER, respiratory exchange ratio; UCP1, uncoupling protein 1

2 | METHODS

2.1 | Search strategy and identification of studies

Three databases were searched (EMBASE, Web of Science, and PubMed), from the earliest date available to 28 February 2019. A subject heading and keyword search was conducted using three concepts (oestrogen, energy homeostasis, and CNS), which were combined using the AND Boolean operator. Synonyms within each concept were combined using the OR Boolean operator (Appendices S1 and S2). The results were imported into EndNote X8 (Thompson Reuters, USA). Articles were screened using selection criteria (Table 1) initially by title alone, by one reviewer (W.S.). Screening by abstracts was then

TABLE 1 Study selection criteria

Criteria	Determined by
Must contain concept of energy homeostasis	Outcomes
Must contain concept of oestrogen	Intervention
Must be a research article	Research design
Must be a mammalian species	Research design
Must contain at least one outcome measure of metabolic change (only feeding insufficient)	Outcomes
Must be in English	

performed by two independent reviewers (W.S. and C.K. or J.R.). Any differences in opinion on inclusion were discussed until consensus was reached.

2.2 | Intervention

Interventions needed to modulate oestrogen levels (eg, ovariectomy [OVX] and administration of exogenous oestrogen) or oestrogen signalling (eg, ER-KO). Studies were not excluded based on whether oestrogen levels/signalling were increased or decreased.

2.3 | Outcomes

The outcomes needed to include a measure of BAT activity or whole body metabolism in some form as outlined in Figure 1. Temperature, BAT sympathetic nerve discharge, body weight, and indirect calorimetry were all accepted outcome measures. Food intake was considered relevant, even though it is not a measure of metabolism, since it allows some inference as to whether a change in body weight was driven by appetite or a change in metabolic rate. Hence, food intake data were collated only if a measure of body weight was also included in the study.

2.4 | Research design

The article needed to be a research article containing in vivo experiments (exclusively in vitro studies, and reviews were excluded). Articles were not excluded on the basis of gender, sample size, or animal age.

2.5 | Data extraction

Data extraction was completed by one author (W.S.) and checked by second author (C.K. or J.R.). Data pertaining to population, study design, description of intervention, and outcome measures were extracted and compiled in a spread sheet. Where data were not provided numerically, it was estimated based on graphs presented. If data were not presented numerically or graphically, authors were contacted to request data.

2.6 | Quality analysis

Article quality, in terms of risk of bias, was assessed with the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool.[15] This tool was adapted from the Cochrane risk of bias tool, specifically for animal intervention studies. SYRCLE's risk of bias tool uses a total of 10 items to assess selection, performance, detection, attrition, and reporting biases. Each of the 10 items was scored as low, high, or unclear risk of bias. Articles were not excluded from this review on the basis of quality. The quality of articles was used to inform the weight to give each set of results when collating and interpreting data.

2.7 | Data synthesis

Data for outcome measures that were reported in sufficient detail were then transferred to Review Manager Version 5.3 (RevMan) for meta-analysis. Due to a mixture of various scales being reported to measure the same outcome, standard mean difference (SMD) with 95% confidence interval (CI) was used to calculate effect sizes.[16] In order to incorporate heterogeneity among studies, a random effects model was used.[16] Additionally, the I^2 value was used to assess heterogeneity. An I^2 value of 100% was considered completely heterogeneous. Values of 75%, 50%, and 25% indicated high, moderate, and low heterogeneity, respectively.[17] Articles were grouped by the population characteristics, and the outcome measures of interest were recorded (Table 2). Species- and sex-specific meta-analyses were performed in order to identify any potential species or sexual dimorphisms.

TABLE 2 Populations and variables for comparison by meta-analysis

Population	Treatment Groups	Outcome Measures
OVX female rats	Control	Body weight (change from baseline in grams)
OVX female mice	Experimental	Body weight (final in grams)
Intact female rats		Body weight (percentage change from baseline)
Intact female mice		
Intact male mice		

3 | RESULTS

3.1 | Yield

A total of 10 008 articles were identified through database searches (Figure 2). Of these, 2913 were duplicates. Citation tracking and reference checking yielded 13 additional articles. Inclusion/exclusion criteria (Table 1) were applied to the titles of 7108 articles and as a result 6196 articles were excluded. The inclusion/exclusion criteria (Table 1) were then applied to the abstracts of the remaining 912 articles, resulting in 812 articles being excluded. One hundred articles underwent full-text screening, and of these, 67 were included in this review.[7,8,10,11,18-80] Articles excluded during full-text screening and reasons for exclusion can be found in Appendix S3.

3.2 | Characteristics of included studies

Of the 67 studies in the final library, 35 used mice, 27 used rats, four used guinea pigs, and three used Syrian hamsters (Appendix S4). Forty-nine of the included studies used only females, five used only males, while 12 used both males and females. One article did not report the gender of the animals used. Of the studies using females, a large proportion (39 articles) used ovariectomy as a part of their experimental design. Body weight was the most common outcome

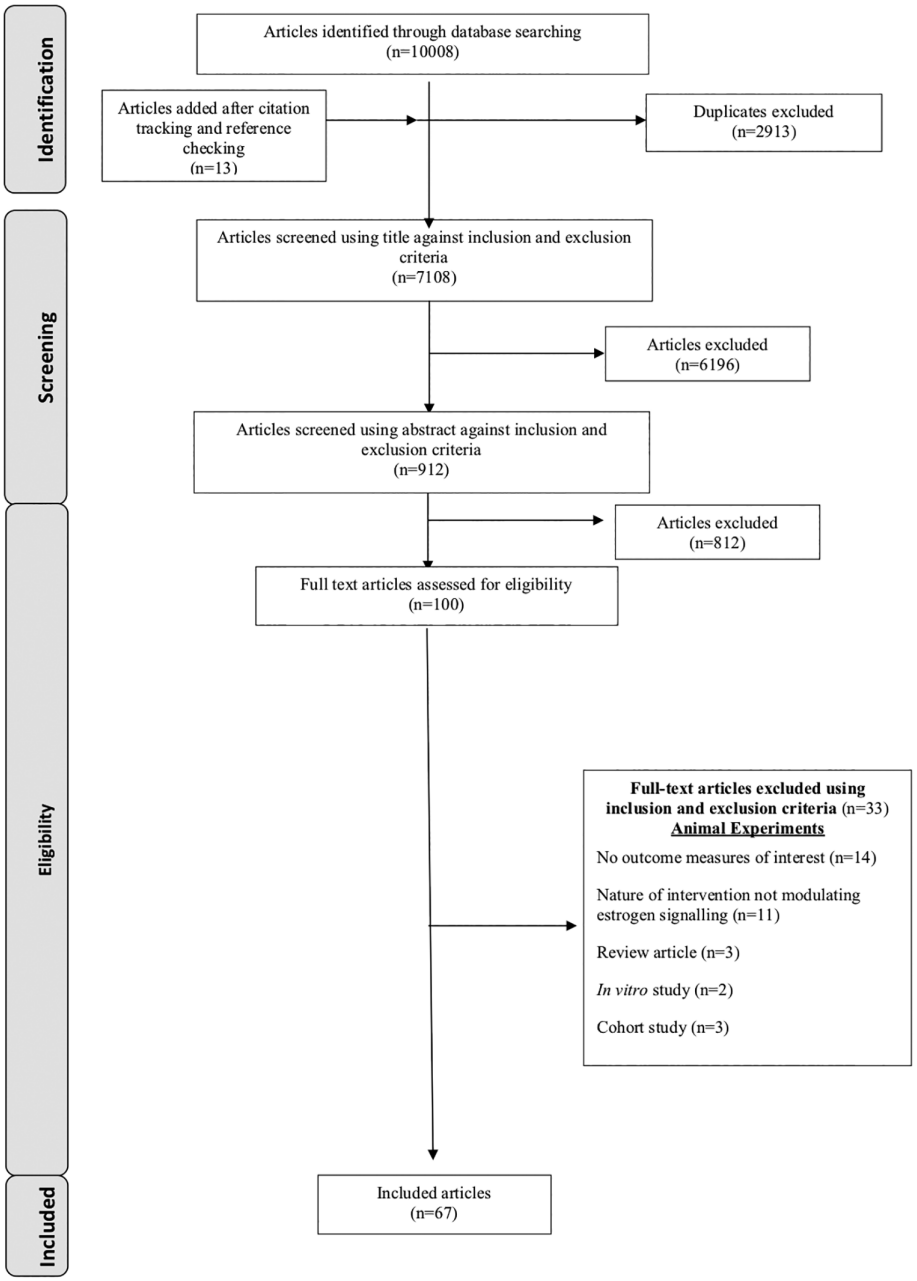

FIGURE 2 PRISMA flowchart summarizing the yield of the search strategy and screening procedures

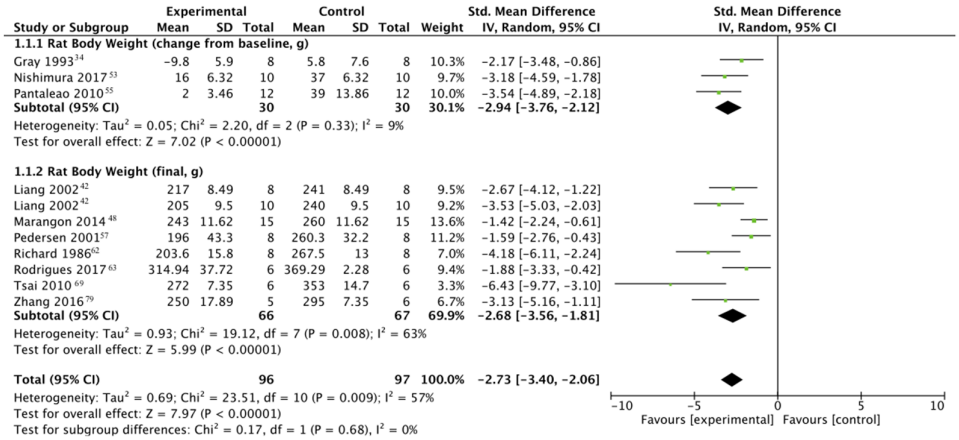

FIGURE 3 Effect of oestrogen (experimental) on attenuation of body weight gain between ovariectomized female rats

measure reported (61 articles), closely followed by food intake (47 articles).

3.3 | Quality

For items 1, 3, 4, 5, 6, and 7 in the SYRCLE's risk of bias tool,[15] the majority of articles were deemed to have an unclear risk of bias because relevant information was not reported (Appendix S5). Of the 67 included studies, 28 (41.8%) did not adequately address incomplete outcome data, five (7.5%) did not adequately generate their allocation sequence, four (6.0%) were not "free of other problems that could result in a high risk of bias," three (4.5%) used groups that were not similar at baseline or not adjusted for confounders, three (4.5%) were not free of selective outcome reporting, and two (3.0%) did not adequately conceal group allocation (Appendix S5).

3.4 | Effect of oestrogen in ovariectomized females

Of the included studies, five studies performed ovariectomy, with no subsequent oestrogen administration, as the experimental group.[28,38,39,66,73] Of these five studies, three reported a significant increase in the body weight of mice and rats subsequent to ovariectomy,[28,66,73] and two reported no significant change in the body weight of rats and Syrian hamsters.[38,39] Several studies also implemented ovariectomy, followed by administering exogenous oestrogen, or an oestrogen analogue. Nineteen single studies,* utilizing oestrogen supplemented ovariectomized rodents as the experimental group, could not be included in the meta-analysis (Appendix S4). Of these studies, only Martinez de Morentin et al[7] measured a significant increase in sympathetic nerve activity to BAT in the oestrogen treated group. While Mamounis et al[46] reported no significant change to heat production, Borgquist et al[24] reported a significant decrease in heat production and oxygen consumption, subsequent to ovariectomy and exogenous oestrogen. The remaining individual studies reported body weight and concurred with the findings of the meta-analysis but were devoid of the obvious species differences seen in the meta-analysis (Appendix S4, Figures 3† and 4‡). Of these individual studies, 15 reported a significant attenuation of weight gain in the oestrogen-supplemented group,§ three reported no significant difference in body weight,[19,46,67] and one study reported an increase in body weight.[77]

A meta-analysis could only be conducted when sufficient studies administered exogenous oestrogen post ovariectomy and reported body weight outcomes. Results of the meta-analyses suggest that exogenous oestrogen attenuated weight gain, in ovariectomized rats (Figure 3). However, no significant attenuation was observed in ovariectomized mice (Figure 4).

3.5 | Effect of oestrogen in gonad-intact females and males

Several studies reported on the effects of exogenous oestrogen, or an oestrogen analogue, in gonad-intact mice and rats. Nine single studies that could not be included in the meta-analysis analysed the effect of oestrogen in gonad-intact animals (Appendix S4).¶ Batista et al[20] indicated reduced heat production in mice compared with the control group. In contrast, MacKay et al[11] indicated a significant increase in energy expenditure following administration of bisphenol A (BPA) to male mice. One additional study[11] reported no significant change to energy expenditure in female mice. Four studies reported a decrease in body weight, upon administration of exogenous oestrogen in mice[23,31,43] and rats,[59] while four reported no significant difference in body weight between treatment groups in mice[11,18,45] and rats.[22] In the six studies that investigated the effects of exogenous oestrogen in male mice and rats,[11,20,27,45,50,70] two reported a decrease in body weight, upon administration of exogenous oestrogen in mice[27] and rats,[70] while two others reported no significant difference in body weight between treatment groups in mice.[11,45] The study of Miyawaki

*References 7, 19, 29, 32, 33, 37, 41, 46, 49, 52, 54, 57, 60, 62, 64, 67, 71, 77, 78.

†References 34, 42, 48, 53, 55, 57, 62, 63, 69, 79.

‡References 10, 40, 46, 76, 80

§References 7, 29, 32, 33, 37, 41, 49, 52, 54, 57, 60, 62, 64, 71, 78.

¶References 11, 18, 22, 23, 31, 43, 45, 50, 59.

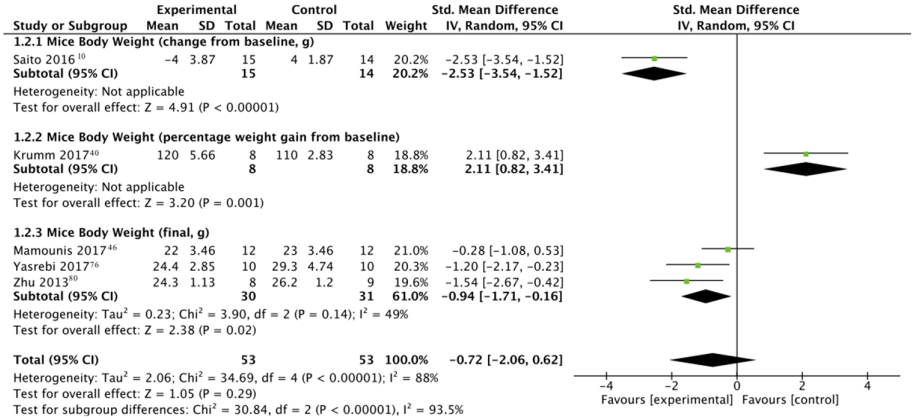

FIGURE 4 Effect of oestrogen (experimental) on attenuation of body weight gain between ovariectomized female mice

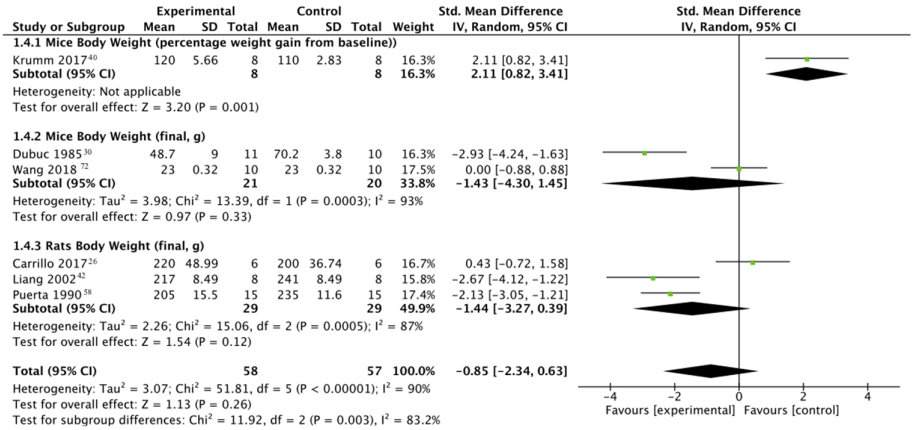

FIGURE 5 Effect of oestrogen (experimental) on attenuation of body weight gain between gonad-intact female mice and rats

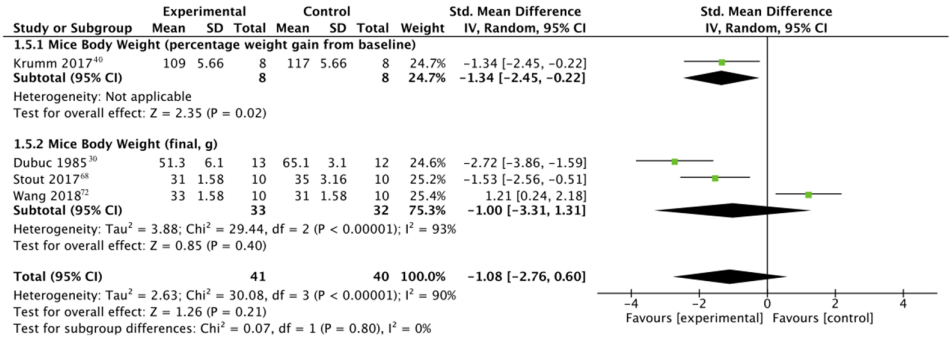

FIGURE 6 Effect of oestrogen (experimental) on attenuation of body weight gain between gonad-intact male mice and rats

et al[50] was the only article that reported an increase in body weight in mice.

The results of the meta-analyses for mice and rats for this intervention suggest that oestrogen had no significant effect on body weight in either gonad-intact female mice and rats (Figure 5[**]) or male mice (Figure 6[††]).

3.6 | Oestrogen receptor knockout

Multiple studies used ER-KO animals. Most frequently, NR3A1 was knocked out, with nine studies implementing this as their intervention. Although a meta-analysis could not be conducted, eight of the nine studies report an increase in body weight in both males and females subsequent to NR3A1-KO.[§§] Liver-specific NR3A1-KO animals demonstrated no significant change in body weight relative to wild type.[21]

[**]References 26, 30, 40, 42, 59, 72, 81.

[††]References 30, 40, 68, 72, 81

[§§]References 35, 36, 51, 56, 61, 65, 74, 75.

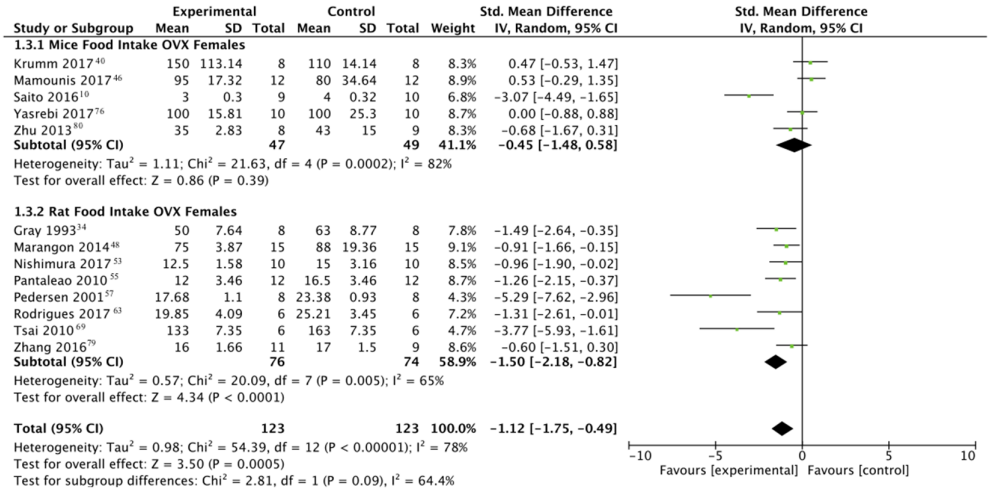

FIGURE 7 Effect of oestrogen (experimental) on food intake between ovariectomized female mice and rats

Only one study used oestrogen receptor beta knockout (NR3A2-KO) mice,[25] and reported a decrease in body weight for the experimental group, but failed to report the sex of the animals used. One additional study used G protein-coupled oestrogen receptor knockout (GPER-KO) mice[8] and reported a significant increase in body weight for both males and females in the experimental group.

3.7 | Appetite

Meta-analysis analysing the effect of oestrogen in ovariectomized rats and mice identified a relatively consistent and significant reduction of food intake in oestrogen supplemented ovariectomized rats, but not mice (Figure 7[¶¶]).

4 | DISCUSSION

This review identified that data directly related to BAT thermogenesis are limited as are studies reporting indirect measures of metabolic rate. Exogenous oestrogen trended to increase metabolic rate and BAT thermogenesis, although a meta-analysis could not be performed since studies did not report on similar outcome measures. Exogenous oestrogen administration, to ovariectomized rodents, attenuated weight gain and increased metabolic rate in rats and possibly mice. Administration of exogenous oestrogen to gonad-intact females yielded more varied data than ovariectomized animals. Gonad-intact male rats and mice chronically administered with exogenous oestrogen also weighed less than control animals. Changes in body weight could not be accounted for solely by metabolic mechanisms; it would appear that changes in feeding were also contributing to modulation of body weight.

Results from the meta-analysis and individual studies not included in the meta-analysis in this review identified that ovariectomy causes weight gain, which can be negated by administration of exogenous oestrogen (Figures 3 and 4). Data pertaining to whether exogenous oestrogen elicits weight loss in gonad-intact females contained more discrepancies. These discrepancies for gonad-intact animals were also observed in our meta-analysis (Figure 5) and the individual studies[***] that could not be included in the meta-analysis.

Similar to gonad-intact females, data pertaining to oestrogen's effects in gonad-intact males also contained discrepancies, as evidenced by our meta-analyses (Figure 6) and variable findings in individual studies.[11,20,27,45,50,70]

Although the ratio of studies reporting weight loss to those reporting no weight loss, in gonad-intact males and females appear to be similar, the physiological mechanisms behind these observations may not be the same. A previous study analysing the direct effects of sex hormones on BAT[9] identified that oestrogen modulated the expression of adrenergic receptors (ARs) in BAT, such that β_3-AR mRNA and protein were up-regulated, and α_{2A}-AR mRNA and protein were down-regulated. This resulted in a larger and more prolonged response to sympathetic activation by norepinephrine. Therefore, in gonad-intact females, metabolic response to oestrogen may have a ceiling effect that exogenous oestrogen cannot overcome. The converse was observed upon administration of testosterone; β_3-AR mRNA and protein were down-regulated, and α_{2A}-AR mRNA and protein were up-regulated,[9] leading to smaller and shorter responses to sympathetic activity evoked norepinephrine. Therefore, in gonad-intact males, the expression ratio of ARs may result in the BAT being more resistant to sympathetic activation.

While metabolic data from individual studies, collected in this review, contained discrepancies, greater weight can be placed on more direct measures, as alluded to in Figure 1 and in our assessment of risk of bias. Nerve recording, as performed by Martinez de Morentin et al,[7] is a very direct and sensitive measure of sympathetic nerve discharge to BAT. This outcome has also been strongly correlated with increased BAT temperature and expired CO_2.[82] Additionally, Martinez de Morentin et al[7] was assessed to have a low risk of bias under every item for which there was sufficient information

[¶¶]References 10, 34, 40, 46, 48, 53, 55, 57, 63, 69, 76, 79-81.

[***]References 11, 18, 22, 23, 31, 43, 45, 50, 58.

(Appendix S5). This study reported increased activity along the nerve branch that innervates interscapular BAT (iBAT nerve), following administration of exogenous oestrogen in ovariectomized animals. This provides strong evidence that exogenous oestrogen increases sympathetic nerve drive to BAT, via oestrogen's effects in the CNS.

Both BAT metabolism and appetite are being modulated by the CNS via the intracellular adenosine monophosphate-activated protein kinase (AMPK) signalling pathway, in the hypothalamus.[7] Specifically, metabolism seems to be mediated by neurons in the ventromedial hypothalamus (VMH), while feeding is controlled by neurons of the arcuate nucleus (ARC).[7] Selective knockout of NR3A1 in hypothalamic pro-opiomelanocortin (POMC) neurons (which suppress feeding behaviour) leads to increased feeding and weight gain.[75] Additionally, selective knockout of NR3A1 in neurons coexpressing steroidogenic factor-1 (SF1) demonstrated reduced BAT thermogenesis as measured by UCP1 expression in BAT.[75] These data suggest that the activation of distinct populations of NR3A1-expressing cells in the brain are involved in body weight and metabolic regulation. However, not all details of this signalling pathway are clear. Findings in this review suggest that the GPER and NR3A1 are involved in oestrogen-mediated metabolic changes.[†††]

Further elucidation of the receptors and signalling pathway for oestrogen-mediated changes in metabolism is of great clinical relevance. For instance, there is a correlation between menopause and increased prevalence of the metabolic syndrome.[83] While hormone-replacement therapy has been implicated in alleviating aspects of the metabolic syndrome in postmenopausal women,[84] this therapy has also been associated with an increased incidence of breast cancer, stroke, and pulmonary embolism.[85] Selectively targeting the oestrogen-BAT axis (via CNS pathways) might allow alleviation of the metabolic syndrome, while negating the adverse side effects of traditional hormone replacement therapies. Accomplishing this, however, relies upon a comprehensive knowledge of signalling pathways underlying the oestrogen-BAT axis. Promise for agonists that selectively influence this axis has been recently shown.[70] In this study, an oestradiol-glucagon-like peptide 1 (GLP1) conjugate was formed and showed a greater efficacy for reducing body weight and food intake of rats than either component of the conjugate in isolation. If selective activation of the oestrogen-BAT axis can be accomplished, benefits will not only be limited to postmenopausal hormone replacement therapy. Scope may extend to individuals who have undergone an oophorectomy or suffered from polycystic ovarian syndrome.

Beyond women, there exists a gap in the literature surrounding exogenous oestrogen in the castrated male population. This is of clinical relevance as people transitioning from male-to-female and undergoing hormone therapy are reported to suffer an increase in body weight and body fat.[86] Additionally, cross-sex hormone therapy among this transgender population has been correlated with increased cardiovascular morbidity.[87,88]

[†††]References 8, 35, 36, 51, 56, 61, 65, 74, 75.

5 | STRENGTHS AND LIMITATIONS

The systematic nature of our search strategy reduced the likelihood of missing relevant articles. To our knowledge, a meta-analysis has not been performed to investigate the metabolism modulating effects of oestrogen in animal models. Meta-analyses increase statistical power beyond that available in a single study. This is exemplified in Figure 4, where studies with seemingly clear but contrasting outcomes can be consolidated. Few studies reported similar direct outcome measures of BAT metabolism and therefore were unable to be included in the meta-analysis. Limited studies from the final library could be included in a meta-analysis, usually because *n* values were reported as a range rather than discrete values for each group. There were also deficits in reporting sufficient detail for accurate assessment of risk of bias that may have influenced the final findings presented in this review.

6 | CONCLUSION

Oestrogen seemingly has the capacity to stimulate BAT thermogenesis, in ovariectomized female rats and possibly mice. This increase in thermogenesis, along with appetite suppression, appears to attenuate postovariectomy bodyweight gain. Although these observations are relatively well supported in ovariectomized animal models, the effects of exogenous oestrogen in gonad-intact male and female rodents are less robust.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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