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REVIEW

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Impact of estrogens on resting energy expenditure: A systematic review

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Summary

The fear of weight gain is one of the main reasons for women not to initiate or to early discontinue hormonal contraception or menopausal hormone therapy. Resting energy expenditure is by far the largest component and the most important determinant of total energy expenditure. Given that low resting energy expenditure is a confirmed predictive factor for weight gain and consecutively for the development of obesity, research into the influence of sex steroids on resting energy expenditure is a particularly exciting area. The objective of this systematic review was to evaluate the effects of medication with natural and synthetic estrogens on resting energy expenditure in healthy normal weight and overweight women. Through complex systematic literature searches, a total of 10 studies were identified that investigated the effects of medication with estrogens on resting energy expenditure. Our results demonstrate that estrogen administration increases resting energy expenditure by up to +208 kcal per day in the context of contraception and by up to +222 kcal per day in the context of menopausal hormone therapy, suggesting a preventive effect of circulating estrogen levels and estrogen administration on weight gain and obesity development.

KEYWORDS
estrogen, hormonal contraception, menopausal hormone therapy, resting energy expenditure

1 | INTRODUCTION

1.1 | Obesity, basic facts, and considerations

Obesity shows a concerningly high and, most importantly, continuously increasing prevalence. The proportion of overweight (BMI ≥ 25 kg/m^2) people aged 18 years and older worldwide has almost doubled in the last 40 years: In 1975, 21.5% of the adult population was estimated to be overweight; by 2016, this number had risen to 38.9%. The proportion of obese (BMI ≥ 30 kg/m^2) adults had even tripled, from an estimation of 4.7% in 1975 to 13.1% in 2016.[1] Obesity is a commonly known major risk factor for morbidity and mortality,[2–5] which may even lead to a stagnation or decline in life expectancy.[6]

The fear of unwanted weight gain is one of the main reasons for women not to initiate or to early discontinue hormonal contraception

Abbreviations: AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BAT, brown adipose tissue; CEE, conjugated equine estrogens; CNS, central nervous system; DEE, dietary energy expenditure; E2, estradiol; EE, ethinyl estradiol; EI, energy intake; ER, endoplasmatic reticulum; ERα, estrogen receptor α; HC, hormonal contraception; MHT, menopausal hormone therapy; OC, oral contraceptive; PAEE, physical activity energy expenditure; REE, resting energy expenditure; SNS, sympathetic nervous system; TEE, total energy expenditure; UCP1, uncoupling protein 1; VMH, ventromedial hypothalamus; WAT, white adipose tissue; β3 AR, β3 adrenergic receptor.

(HC) or menopausal hormone therapy (MHT).[7–11] According to current data, however, this concern seems to be unfounded. Neither a sex hormone-related significant weight-increasing nor weight-reducing effect has been clearly confirmed or refuted. Cochrane analyses on the topic of the influence of combination contraceptives,[12] progestin-only contraceptives,[13] and MHT[14] on body weight showed no association between sex hormone use and weight changes. However, the duration of hormone administration in the majority of the studies included in these Cochrane analyses was probably too short to detect significant effects of sex hormone medication on body weight. Overall, the majority of studies lack clear evidence to definitively rule out the possibility of sex hormone-induced weight change.

Obesity is the result of a chronic disturbance in energy homeostasis caused by an imbalance between energy intake (EI) and total energy expenditure (TEE). The term "energy intake" is almost self-explanatory and refers to the intake of energy through macronutrients (carbohydrates, proteins, fats) and alcohol, whereas the term "total energy expenditure" is a more complex one and consists of three main components: first, resting energy expenditure (REE); second, dietary energy expenditure (DEE, also called "thermic effect of food" or "diet-induced thermogenesis"); and third, physical activity energy expenditure (PAEE).[15–17] REE represents the largest component of TEE (60%–80%[18–20]) and is defined as the metabolic rate required to maintain vital physiological functions from the cellular to the systemic level of an organism that is awake, in mental and physical rest, fasting, and in a thermoneutral environment.[15–17] DEE describes the energy required for the digestion, absorption, and storage of ingested nutrients. For individuals consuming an average mixed diet, DEE amounts to approximately 10% of TEE.[15,16,18,21] PAEE is the most variable component of TEE and can be significantly increased by intentional physical exercise. Given the typically sedentary lifestyle of Western societies, it averages 25%–35%[22] of TEE ranging from 15% in very inactive individuals to up to 50% in highly active individuals.[18]

Both a reduction in EI and an increase in PAEE are necessary for sustainable weight loss but are difficult to implement in the long term. For this reason, research has recently focused increasingly on the possibility of achieving a negative energy balance by increasing REE.

1.2 | Resting energy expenditure and basal proton leak

As mentioned above, REE is defined as the energy required by an organism to maintain homeostasis.[15–17] The majority of the energy required for REE is generated through the breakdown of organic substrates in the course of cellular respiration in the mitochondria. The goal of cellular respiration is to produce adenosine triphosphate (ATP), the universal energy source for cellular functions. The main part of ATP production takes place in the respiratory chain, the final step of cellular respiration. However, the coupling of oxidative processes to ATP production has limited efficiency. Part of the energy of the proton motive force is "lost" through a basal proton leak at the inner mitochondrial membrane and is thus uncoupled from ATP production and directly converted into heat. Hence, REE is the sum of the energy required for ATP production (about 70%–80% of REE) on the one hand, and the energy converted into heat through the basal proton leak (20%–30% of REE), on the other.[22–28] The latter enables the organism to maintain body temperature in a thermoneutral situation without the need to actively initiate other homeostatic thermoregulatory mechanisms.[29,30] The basal proton leak accounts for a significant proportion of this so-called obligatory thermogenesis.[27,31,32] Still, the exact mechanism behind this process remains controversial.[33] However, reinforcing the process of "wasting" energy through proton leaks represents a possibility to modulate the energy balance toward the negative and is therefore considered a potential and promising target for the treatment of obesity. Whereas the basal mitochondrial proton leak cannot be intentionally modulated, there is an inducible/adaptive/facultative proton leak exclusively in brown adipose tissue (BAT) mitochondria, which, in contrast to the basal proton leak, can directly be regulated due to its dependence on the activity of the tissue-specific so-called uncoupling protein 1 (UCP1).[29,30]

1.3 | Brown adipose tissue and adaptive proton leak

Mammals have two types of adipose tissue that play opposite roles in the body's energy metabolism: white lipid-storing adipose tissue (WAT) and brown lipid-burning adipose tissue. WAT cells contain a single large lipid vacuole and a few mitochondria, whereas BAT cells are characterized by multilocular small lipid droplets and a large number of well-developed mitochondria. WAT not only has the ability to store excess energy in the form of triglycerides and release this energy as needed in the form of free fatty acids but, in recent years, has also gained an expanded role as a metabolically and endocrinologically highly active organ. Through the release of various biochemically active substances, such as adipokines, it is involved in communication between cells, tissues, and organs.[34]

In contrast to energy storage, the main function of BAT is to generate heat on demand through the oxidation of free fatty acids, thus consuming energy. This process is part of the so-called adaptive thermogenesis (synonyms: facultative or nonshivering thermogenesis).[29,30,35,36]

It is the mass of mitochondria in the BAT cells that enables this form of energy release and gives this particular fat tissue its characteristic brown color. In contrast to the regular mitochondria, the BAT mitochondria are characterized by the ability to actively uncouple cellular respiration from the synthesis of ATP and consequently to convert the energy released during fatty acid oxidation directly into heat, circumventing ATP production. This biochemical short circuit is made possible by the unique expression of UCP1, an inducible ion channel at the inner mitochondrial membrane that allows the re-entry of protons, from the intermembrane space into the mitochondrial matrix, bypassing the membrane-bound ATP synthase and thus dissipating the energy of the proton gradient directly into heat, as described previously (Figure 1).[25,29,35]

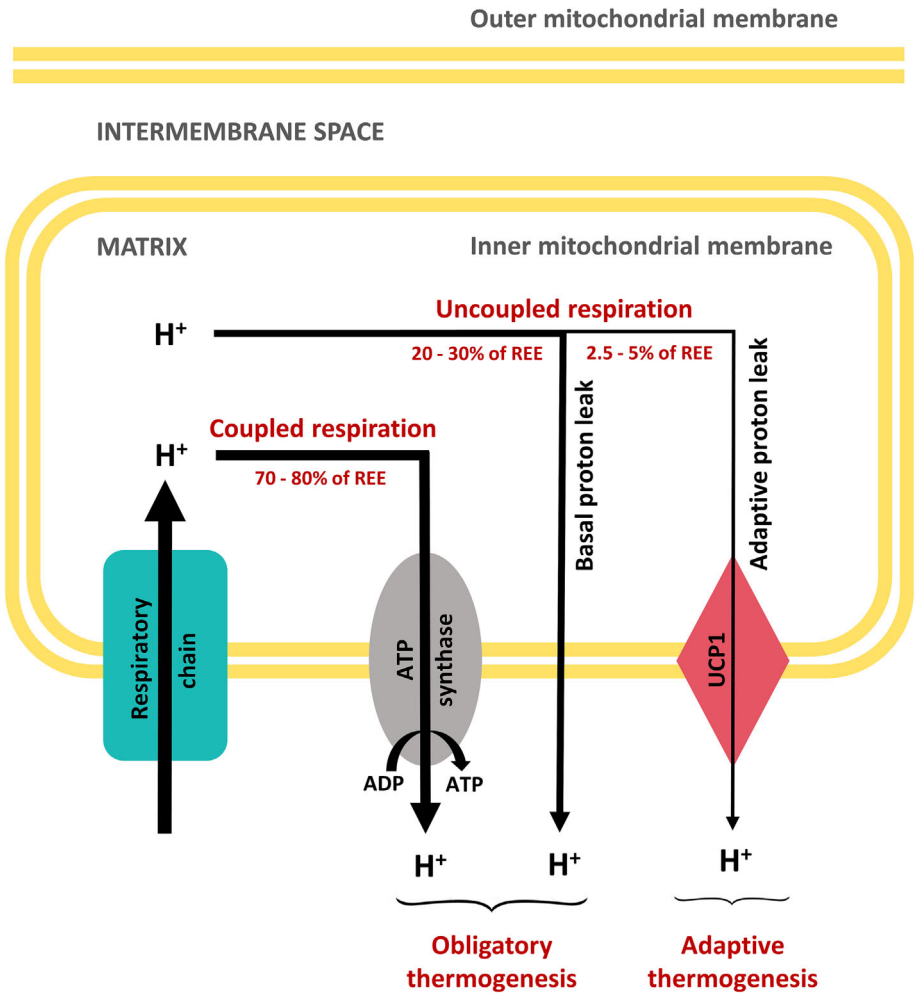


FIGURE 1 Obligatory versus adaptive thermogenesis. The goal of cellular respiration is the production of adenosine triphosphate (ATP), the universal energy source for cellular functions. Only 70%–80% of the energy of the proton motive force is used for ATP production. 20%–30% of this energy is "lost" through a basal proton leak at the inner mitochondrial membrane and is converted directly to heat, thus uncoupling it from ATP production. These two processes together are referred to as obligatory thermogenesis. Although the basal mitochondrial proton leak cannot be intentionally modulated, there is also an adaptive proton leak that, unlike the basal proton leak, can be directly regulated because of its dependence on the activity of the so-called uncoupling protein 1 (UCP1) at the inner mitochondrial membrane. Thus, cellular respiration can be actively uncoupled from ATP synthesis when needed, and the energy released during cellular respiration can be directly converted to heat bypassing ATP production. This process is called adaptive thermogenesis.

The concept of additional stimulation of this energetically wasteful tissue with the resulting increase in energy expenditure and its potential influence to counteract the development of obesity and related diseases has kept scientists busy for more than 40 years.[37] In fact, in animals (rodents), the enhancement of BAT thermogenesis to maintain healthy body weight is now well established.[38–43] In humans, however, it has long been assumed that only infants possess a physiologically relevant amount of BAT.[29,44] Following the recent rediscovery of metabolically active BAT also in adult humans,[45–49] its experimental use has once again attracted increased interest in clinical and non-clinical studies.[38,50–54]

BAT thermogenesis is controlled by the sympathetic nervous system (SNS). The ventromedial nucleus of the hypothalamus (also referred to as the ventromedial hypothalamus, VMH) is the central key center responsible for the regulation of BAT thermogenesis and thus is superior to the SNS.[29,55–58] The physiological stimulus to activate the VMH-SNS-BAT axis is cold.[45,46,49,59–62] Subsequent release of norepinephrine from the SNS leads to activation of BAT via binding to its β3 adrenergic receptors (β3 AR). This is followed by an increase in the activity of intracellular lipolytic enzymes and the breakdown of cytosolic triglycerides to free fatty acids, which are directed into the mitochondria, where they both allosterically disinhibit UCP1 present in the inner mitochondrial membrane and themselves serve as fuel for fatty acid oxidation. Simultaneously, glucose and fatty acid uptake from the periphery into BAT cells is increased to replenish intracellular lipid stores.[29,30,35,49] Hence, the BAT is the only tissue that can literally "burn fat."

However, stimulation of the BAT by the SNS leads not only to an increase in its metabolic activity but also to an expansion of its volume as well as to the so-called "browning," which refers to the recruitment of brown adipocytes by differentiation from brown adipocyte precursors/preadipocytes in WAT or by transdifferentiation of existing white adipocytes. These stimulation-induced thermogenically competent cells in WAT are referred to as brite (brown-in-white) or beige adipocytes. As the name implies, they exhibit phenotypic and functional features common to white and brown adipocytes. In summary, BAT is a flexible tissue that can be recruited by specific triggers and atrophies in their absence.[35,38,53,56,58,63,64]

There is growing evidence that BAT volume and activity in humans are associated with increased energy expenditure,[46,51,65–67] decreased BMI[45–47,68–71] as wells as improved glucose,[72–75] and lipid metabolism.[73,75] Thus, people with a higher volume of metabolically active BAT also appear to be more likely to be protected from developing obesity and its related diseases.

Because more or less intensive, intermittent as well as continuous cold stimuli are not tolerable for humans in the long run to provide continuous activation of the BAT, other substances have been

investigated. Hormonal substances include adrenal steroids,[76] thyroid hormones,[77–80] insulin,[81,82] and estradiol.[83–85]

1.4 | Estrogens and energy metabolism

The function of estrogens as important regulators of energy balance is well established.[86–88] Using the example of ovarian insufficiency, for example, at menopause, as a consequence of ovariectomy or ovarian function suppression, it has been sufficiently demonstrated that low estrogen levels are associated with increased EI[87] and decreased PAEE,[89] hence leading to weight gain and promoting the development of obesity in the long term,[87,90–98] with MHT counteracting this development.[99–101] Furthermore, several studies in premenopausal women show an increase in REE during the luteal phase, when sex steroid levels (estradiol and progesterone) are elevated, compared with the follicular phase,[102–108] when sex steroid levels are low, suggesting a role for sex steroids, particularly estrogens,[109] in the regulation of REE. In contrast, other studies have found no difference in REE at different phases of the menstrual cycle.[110–113] Consequently, if physiological variations of estrogens affect REE, it is reasonable to assume that exogenous administration of these hormones also has an impact on REE. However, data on this are scarce.

1.5 | Estradiol and its central and peripheral effects on brown adipose tissue thermogenesis

Estrogen receptor α (ERα), expressed by both the central nervous system (CNS) and adipose tissue, is considered the key mediator of estrogen action on energy homeostasis.[86,87,114] With respect to energy expenditure, estrogens primarily exert both central and peripheral stimulatory effects on BAT thermogenesis.[84–86,115] Consistent with this is the observation of a sexual dimorphism in the BAT.[116] As far as is currently known, women exhibit greater BAT mass and are more responsive to BAT-activating stimuli than men.[47,117–120] Moreover, these sex differences disappear after menopause.[121,122]

In the CNS, estrogens exert their multiple functions in energy balance by binding to ERα, which is expressed at a variety of sites, predominantly in the hypothalamus.[123–125] The most important actions of estrogens on energy expenditure, in particular on BAT thermogenesis, take place nucleus-specifically in the VMH. Any electrical, pharmacological, and hormonal stimulation of this nucleus increases sympathetic outflow to the BAT via intermediate interconnections in brainstem areas such as the nucleus raphe pallidus and the inferior olive, thereby increasing BAT thermogenesis.[55,58,83,126–129]

Among the major molecular mechanisms mediating the action of estrogens in the hypothalamus is the inhibition of hypothalamic AMP-activated protein kinase (AMPK).[83] AMPK is an enzyme that plays a key role in regulating cellular processes in situations of cellular energy deficiency. Central activation of AMPK leads to an increase in energy production, that is, synthesis of ATP, and a decrease in energy wasting, ensuring the maintenance of cellular energy homeostasis.[130–134] Thus, centrally, estrogens lead to increased sympathetic tone via central inhibition of AMPK, with subsequent activation of BAT thermogenesis and energy "wasting."[83] Other substances known for their effects on metabolic homeostasis and whose common pathway is to increase BAT-specific energy expenditure via AMPK inhibition in the VMH include leptin, thyroid hormones, nicotine, bone morphogenetic protein 8b, and glucagon-like peptide 1 and its analogs.[78,126,135–137] Finally, recent data have shown that not only BAT activation but also the browning of WAT is regulated via AMPK inhibition in the VMH.[115]

Another key mechanism by which estrogens lead to an increase in sympathetic tone and thus activation of BAT and energy wasting is through modulation of the lipotoxic effects of reactive lipid species in the VMH. The deposition of lipophilic metabolites such as ceramides in the VMH associated with overeating, also known as hypothalamic lipotoxicity, leads to the impairment of various cellular functions such as the triggering of stress in the endoplasmic reticulum (ER). The result is reduced sympathetic tone, which leads to reduced BAT thermogenesis and food-independent weight gain.[138] It has been demonstrated that centrally administered estradiol (E2) can counteract the central dysregulation of the energy metabolism triggered by the accumulation of lipid metabolites in the hypothalamus. The binding of E2 to ERα results in a selective reduction of ceramide-induced lipotoxicity and consequently of ER stress in neuronal cells of the VMH, which in turn leads to a markedly increased BAT activity, weight loss, and improvement of glucose metabolism.[139,140]

Peripherally estrogen modulation of BAT occurs by a direct action on ERα in adipocytes. As in the CNS, the effect of estrogens in adipocytes is mediated by AMPK. In contrast to central regulation, in the periphery, AMPK is activated by the binding of estrogen to its receptor. As in BAT triggered by the binding of norepinephrine to the β3-AR, activation of ERα in WAT leads to intracellular lipolysis with release of free fatty acids followed by disinhibition of UCP1. Furthermore, estrogen activity in white adipocytes leads to the expression of BAT-specific genes (e.g., of β3 AR and other markers for mitochondrial biogenesis) and consequently to browning (Figure 2).[141]

The mechanisms underlying estrogen-induced BAT thermogenesis described herein suggest promising clinical effects on REE, body weight development, and glucose and lipid metabolism. To date, results on this topic have almost exclusively come from animal studies, whereas findings in humans are still sparse and inconclusive.

Thus, the aim of this systematic review was to evaluate the effects of medication with natural and synthetic estrogens on REE in healthy normal weight and overweight (BMI 18.5–29.9 kg/m^2) women.

2 | METHODS

2.1 | Information sources and search strategy

The systematic review was registered in PROSPERO, an international database of prospectively registered systematic reviews. To identify all potentially relevant documents on the topic, complex literature searches were designed and executed by a medical information specialist (HJ) according to the guidelines of PRISMA 2020[142] and PRISMA-Search[143] in the following information sources: Medline

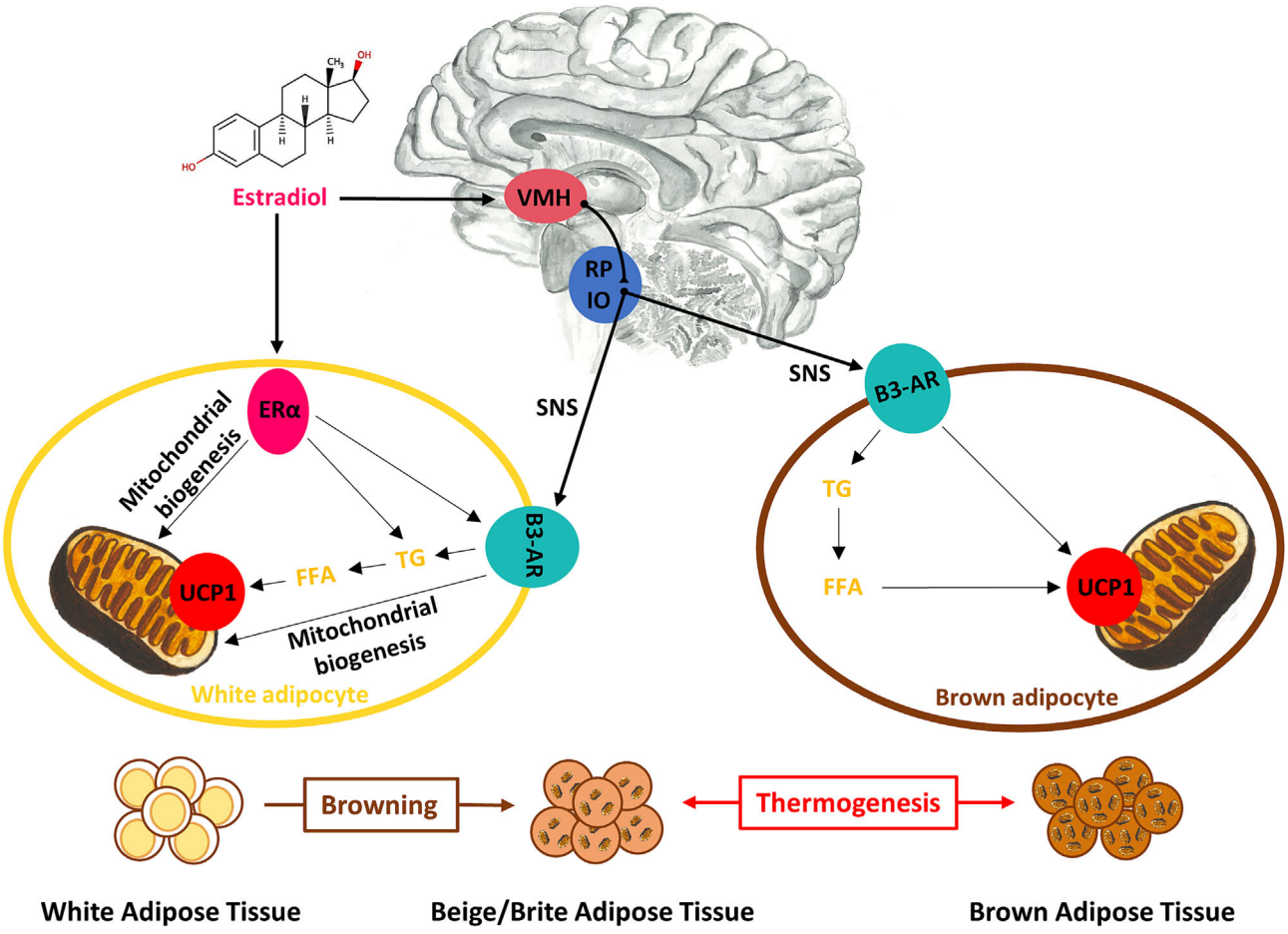


FIGURE 2 Estradiol and its central and peripheral effects on brown adipose tissue thermogenesis. Binding of estradiol (E2) to estrogen receptor α (ERα), expressed by both the central nervous system (CNS) and the adipose tissue, exerts stimulatory effects on brown adipose tissue (BAT) thermogenesis. Centrally, estradiol leads to increased sympathetic nervous system (SNS) activity by binding to its receptor in the ventromedial hypothalamus (VMH) and via intermediate connections in brainstem areas such as the nucleus raphe pallidus (RP) and the inferior olive (IO). Ultimately, triggered by the binding of noradrenaline to the β3 adrenergic receptor (β3 AR), intracellular lipolysis occurs in the BAT and white adipose tissue (WAT) with release of free fatty acids (FF) from triglycerides (TG), followed by disinhibition of UCP1. However, stimulation of the BAT by the SNS not only leads to an increase in its metabolic activity but also to an expansion of its volume as well as to the so-called "browning" of WAT. In the periphery, estradiol leads directly to metabolic activation and browning of WAT via binding to the ERα.

(1946–March 16, 2021), Embase (1974–March 16, 2021), CINAHL (1937–March 16, 2021), Cochrane Library (1996–March 16, 2021), Web of Science (1900–March 16, 2021), and ClinicalTrials.gov (NLM).

The searches were conducted on March 17 and 18, 2021. The search concepts used were (1) "women" (of all ages), (2) "resting energy expenditure"/"basal metabolic rate," and (3) "gonadal steroids" (including androgens, estrogens, and progestogens as well as natural and synthetic hormones). In addition to electronic database searching, reference lists and bibliographies from relevant publications were checked for relevant studies. The final detailed search strategies are presented in the Supporting Information.

2.2 | Study selection process

The search strategy yielded a total of 973 articles published between 1929 and 2021. After the removal of duplicates by HJ 429, unique articles were identified. Titles, abstracts, and full texts were double-screened independently by the authors SW and KW and tested against the inclusion criteria. Disagreements between individual judgments were resolved in a bilateral discussion. All English-, German-, or French-language clinical trials that investigated the effects of medication with natural and synthetic estrogens on REE in healthy normal-weight and overweight (BMI 18.5–29.9 kg/m^2) women were included (Figure 3).

2.3 | Data extraction

Relevant information from the included studies was collected for data extraction according to a predesigned protocol established by the two reviewers (SW and KW). For all studies, predefined study data (see Tables 1 and 2) were collected independently by the two reviewers (SW and KW), tabulated according to the PICO elements,

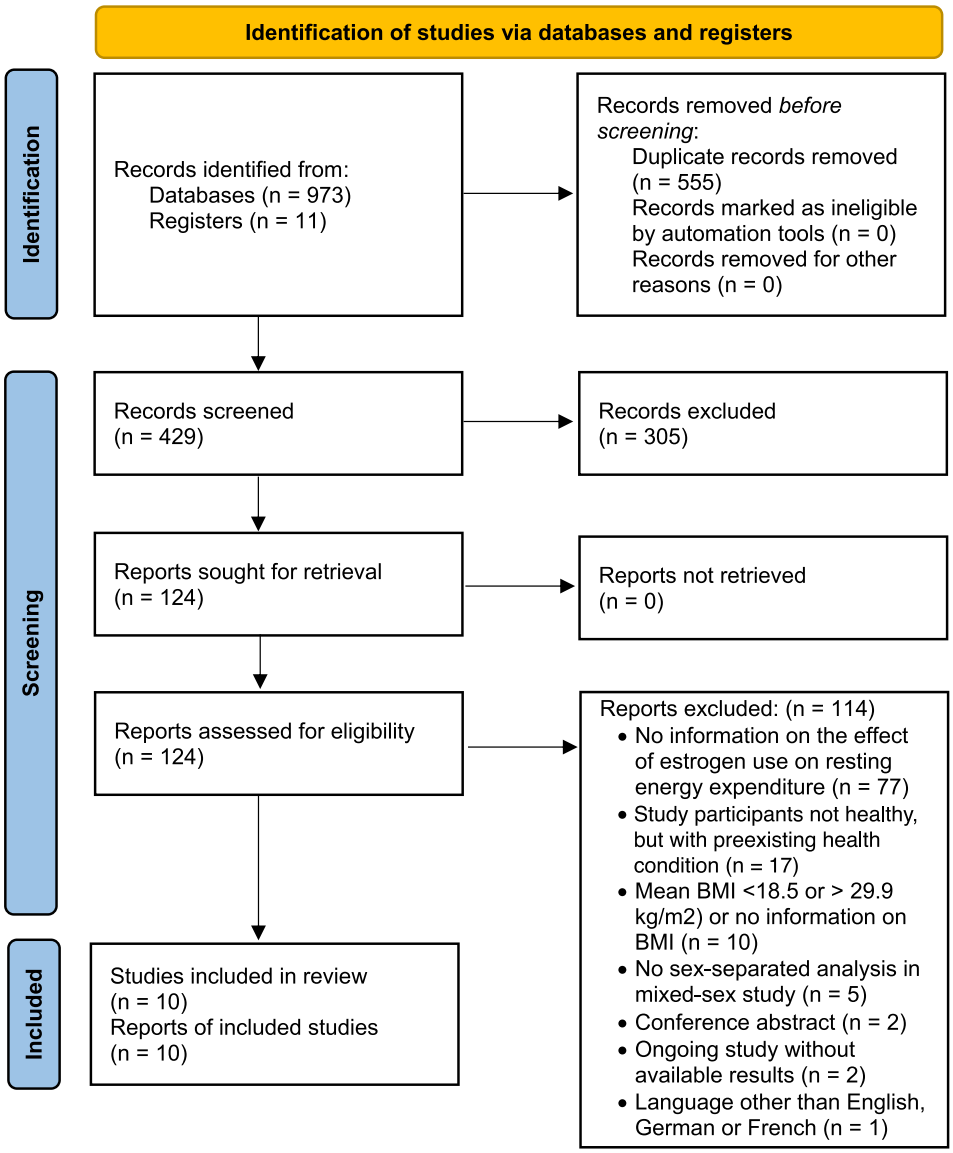


FIGURE 3 PRISMA 2020 flow diagram.

among others, and then cross-checked against each other to ensure correct data collection. The main result of interest, the change in REE as a result of estrogen medication, was expressed variously in the different studies, either in absolute numbers, in *p*-values to indicate the significance of differences, or in purely literal textual terms.

2.4 | Data analysis and risk of bias assessment

The risk of bias was assessed for all included randomized controlled trials (RCTs) using the Cochrane Risk of Bias 2 (RoB 2) tool[144] and for all other included non-RCTs using the Thomas H. Quality assessment tool for quantitative studies,[145] which is independent of study design. All included studies were reviewed by two of the review authors (SW and KW) to independently assess the risk of bias (assessment of methodological quality). Disagreements were resolved by bilateral consensus. With the exception of the study by Eck et al.[146] in which the methodological quality was rated as strong, corresponding to a low risk of bias, the methodological quality of all other studies[147–154] was only rated as moderate (Tables 3 and 4).

3 | RESULTS

3.1 | Characteristics of included articles

Our systematic review identified a total of 10 studies investigating the effects of medication with natural and synthetic estrogens on REE and encompassing 461 healthy normal-weight and overweight women (Tables 1 and 2).[146–155] The 10 included studies consisted of six studies in which estrogens were used in the context of HC[146,149–152,154] and four studies in which estrogens were used in the context of MHT.[147,148,153,155] Study designs were either RCTs,[150,151,153] prospective cohort studies,[147] or cross-sectional studies.[146,148,149,152,154,155] The sample size of each cohort with the population of interest ranged from 6[155] to 99 subjects.[152] The type of

TABLE 1 Overview over the basic characteristics of the included studies.

Author, year of publication, journal	Country	Title	Study design	Primary objective	Population of interest	Groups of interest	Number of participants	Age of participants, years (mean ± SD)	BMI, kg/m^2 (mean ± SD)
Duhita et al., 2019, Nutrients	Switzerland, New Zealand	Assessment of the Dose–Response Relationship between Meal Protein Content and Postprandial Thermogenesis: Effect of Sex and the Oral Contraceptive Pill	RCT	Effect of sex and combined monophasic OC use on the dose–response relationship between meal protein content and dietary-induced thermogenesis, respiratory quotient, hunger, and satiety	Healthy, premenopausal women	OC users OC non-users	7 7	22.6 ± 0.6 24.4 ± 0.9	21.0 ± 0.6 22.8 ± 0.7
Duhita et al., 2017, Obesity	Switzerland	Oral Contraceptive Pill Alters Acute Dietary Protein-Induced Thermogenesis in Young Women	RCT	Effect of menstrual cycle phase and combined monophasic OC use on the dose–response relationship between meal protein content and dietary-induced thermogenesis	Healthy, premenopausal women	OC users OC non-users	8 8	23 ± 1 24 ± 1	21.9 ± 1.2 22.0 ± 0.6
Melanson et al., 2015, J Appl Physiol	USA	Regulation of energy expenditure by estradiol in premenopausal women	RCT	Effects of sex hormone suppression with GnRH-Ag with estradiol vs. placebo add-back therapy for 5 months on total daily energy expenditure and its components	Healthy, premenopausal women	GnRH-Ag + MHT GnRH-Ag + placebo	21 24	33 ± 9 37 ± 8	26.9 ± 6.2 27.3 ± 6.2

(Continues)

TABLE 1 (Continued)

Author, year of publication, journal	Country	Title	Study design	Primary objective	Population of interest	Groups of interest	Number of participants	Age of participants, years (mean ± SD)	BMI, kg/m^2 (mean ± SD)
Aubertin-Leheudre et al., 2008, J Aging Phys Act	Canada	Enhanced Rate of Resting Energy Expenditure in Women Using Hormone-Replacement Therapy: Preliminary Results	Cross-sectional study	Effect of long-term MHT treatment (>1 year) on total daily energy expenditure and its components as well as, body composition in actual MHT-users vs. MHT never-users	Healthy, postmenopausal women	MHT users MHT never-users	13 13	59.2 ± 3.1 59.6 ± 2.7	24.1 ± 2.6 23.7 ± 2.9
Reimer et al., 2005, Physiol Behav	Canada	Dietary and metabolic differences in pre- versus postmenopausal women taking or not taking hormone replacement therapy	Cross-sectional study	Dietary intake analysis in premenopausal women during the luteal and follicular phases as well as in postmenopausal MHT users and never-users	Healthy, postmenopausal women	MHT users MHT never-users	6 7	54.5 ± 1.0 53.4 ± 1.7	26.3 ± 2.0 22.9 ± 1.2
Anderson et al., 2001, Metabolism	USA	Body Composition and Energy Balance: Lack of Effect of Short-Term Hormone Replacement in Postmenopausal Women	Prospective cohort study	Effect of physiologic MHT on body weight, body composition, and energy balance	Healthy, postmenopausal women	45–55-year-old postmenopausal women before and after initiation of MHT 70–80-year-old postmenopausal women before and after initiation of MHT	18 15	52.4 ± 0.6 72.3 ± 0.6	25.0 ± 0.8 26.2 ± 1.0
Kimm et al., 2001, Am J Epidemiol	USA	Effects of race, cigarette smoking, and use of contraceptive medications on resting energy expenditure in young women	Cross-sectional study	Assessment of racial differences in the effects of cigarette smoking, use of contraceptive medication use, and menstrual cycle on REE in a biracial cohort	Healthy, premenopausal women	Contraception users Contraception non-users	48 99	19.4	24.6 ± 5.0 (white women); 27.8 ± 7.18 (black women)

TABLE 1 (Continued)

Author, year of publication, journal	Country	Title	Study design	Primary objective	Population of interest	Groups of interest	Number of participants	Age of participants, years (mean ± SD)	BMI, kg/m^2 (mean ± SD)
Piers et al., 1997, Eur J Clin Nutr	Australia	The validity of predicting the basal metabolic rate of young Australian men and women	Cross-sectional study	Assessment of the accuracy of different equations for the prediction of the basal metabolic rate of young Australians	Healthy premenopausal women	OC users OC non-users	42 47	24 ± 3 23 ± 2	21.7 ± 2.0 22.2 ± 2.6
Eck et al., 1997, Eur J Clin Nutr	USA	Differences in macronutrient selections in users and nonusers of an oral contraceptive	Cross-sectional study	Effect of menstrual cycle phase and OC use on energy balance and its components	Healthy premenopausal women	OC users OC non-users	17 15	21.7 ± 3.2 19.9 ± 3.1	22.2 ± 2.3 20.8 ± 2.8
Diffey et al., 1997, Br J Nutr	Australia	The effect of oral contraceptive agents on the basal metabolic rate of young women	Cross-sectional study	Effect of OC use on REE in young women	Healthy premenopausal women	OC users OC never-users	24 22	26 ± 3 25 ± 3	21.8 ± 2.4 22.3 ± 2.2

Abbreviations: GnRH-Ag, gonadotropin-releasing hormone agonist; MHT, menopausal hormone therapy; OC, oral contraceptive; RCT, randomized controlled trial; REE, resting energy expenditure.

TABLE 2 Overview of the results of interest of the included studies.

Author, year of publication, journal	Groups of interest	Interventions/ medication details	Method, timing, and way of REE measurements	REE baseline/pre-treatment (mean ± SD)	REE post-treatment (mean ± SD)	*p*-value (ΔREE), unadjusted	*p*-value (ΔREE), adjusted	Outcome of interest: ΔREE
Duhita et al., 2019, Nutrients	OC users	OCs used: comb. monophasic OC formulations differed in terms of EE concentration (mean: 26 ± 3 μg/d) and progestin type and dose	IC. Calc. of baseline REE from the av. of 3 meas's. of REE on 3 different d in the week following withdrawal bleeding with an interval of at least 2 d between each meas.	0.89 ± 0.03 kcal/min	-	$p = 0.74$ (between groups)	-	Δ OC users vs. OC non-users: −14 kcal/d ≙ −1.1%; $p = 0.74$
	OC non-users	-	IC. Calc. of baseline REE from the av. of 3 meas's. of REE on 3 different d in follicular phase with an interval of at least 2 d between each meas.	0.90 ± 0.03 kcal/min	-			
Duhita et al., 2017, Obesity	OC users	OCs used: comb. monophasic OC formulations differed in terms of EE concentration (EE 20 μg/d: $n = 4$, EE 30-35 μg/d: $n = 4$); no information on type and dose of progestin	IC. Calc. of baseline REE from the av. of 2 meas's. of REE on cycle d 5–12 and 2 meas's. on cycle d 19–26 with an interval of at least 2 d between each meas.	-	-	$p = 0.6$ (between groups)	-	No effect of OC use on REE.
	OC non-users	-	IC. Calc. of baseline REE from the av. of 2 meas's. of REE in follicular phase (cycle d 5–12) and 2 meas's. in luteal phase (cycle d 19–26) with an interval of at least 2 d between each meas.	-	-		-	

TABLE 2 (Continued)

Author, year of publication, journal	Groups of interest	Interventions/ medication details	Method, timing, and way of REE measurements	REE baseline/pre-treatment (mean ± SD)	REE post-treatment (mean ± SD)	*p*-value (ΔREE), unadjusted	*p*-value (ΔREE), adjusted	Outcome of interest: ΔREE
Melanson et al., 2015, J Appl Physiol	GnRH-Ag + E2 (+ MPA)	Leuprolide acetate 3.75 mg i.m. monthly, E2 75 μg/d-transdermal patch + MPA 5 mg/d orally for 12 d every other month (end of month 2 and 4)	IC. Meas. of pre-treatment REE in follicular phase (cycle d 2–6) in most women. Meas. of post-treatment REE after 5 months of sex hormone suppression with E2 add-back therapy.	1456.1 ± 167.9 kcal/d	1462.6 ± 169.8 kcal/d	n.s. (within-group) $p < 0.05$ (between groups)	$p < 0.05$ (between-groups), adj. for changes in FM and FFM	
GnRH-Ag + placebo	Δ within GnRH-Ag + E2: +6 kcal/d; n.s. Δ within GnRH-Ag + placebo: −54 kcal/d ≙ −3.7%; $p \leq 0.05$ Δ GnRH-Ag + placebo vs. GnRH-Ag + E2: −60 kcal/d ≙ −4.1%; $p \leq 0.05$	Leuprolide acetate 3.75 mg i.m. monthly + placebo patch for 5 months	IC. Meas. of pre-treatment REE in follicular phase (cycle d 2–6) in most women. Meas. of post-treatment REE after 5 months of sex hormone suppression.	1455.4 ± 181.4 kcal/d	1401.1 ± 167.9 kcal/d	$p < 0.05$ (within group) $p < 0.05$ (between groups)		
Aubertin-Leheudre et al., 2008, J Aging Phys Act	MHT users	Actual MHT use for at least 1 year; oral: $n = 11$, transdermal: $n = 2$; CEE 0.625 mg/d: $n = 2$, CEE 0.625 mg/d + MPA 2.5 mg/d: $n = 11$; no information on the regime; av. treatment time of MHT 8.8 years (range 4–12 years)	IC. No further details on the calc. of baseline REE.	1392 ± 228 kcal/d	-	$p = 0.038$ (between groups)	$p = 0.05$ (between groups), adj. for total daily energy expenditure and time since menopause	Δ MHT users vs. MHT never-users: +222 kcal/d; $p = 0.038$

(Continues)

TABLE 2 (Continued)

Author, year of publication, journal	Groups of interest	Interventions/ medication details	Method, timing, and way of REE measurements	REE baseline/pre-treatment (mean ± SD)	REE post-treatment (mean ± SD)	*p*-value (ΔREE), unadjusted	*p*-value (ΔREE), adjusted	Outcome of interest: ΔREE
	MHT never-users	-	IC. No further details on the calc. of baseline REE.	1170 ± 283 kcal/d				
Reimer et al., 2005, Physiol Behav	MHT users	Actual MHT use for at least 1 year; estrogen and progestin; no information on type and dose of estrogen and progestin, regime, and type of application; av. 7 years since menopause	IC. No further details on the calc. of baseline REE.	-	-	n.s.	-	No effect of MHT on REE.
	MHT never-users	Av. 4 years since menopause	IC. No further details on the calc. of baseline REE.	-	-			
Anderson et al., 2001, Metabolism	Postmenop. women of 45–55 years, before and after initiation of MHT	First month of MHT: E2 50 μg/d transdermal patch; second month of MHT: E2 50 μg/d transdermal patch + vaginal progesterone 200 mg/d for the final 7 d	IC. No further details on the calc. of REE pre-treatment, after 1 and 2 months of treatment.	6424 ± 170 kJ/d	E2: 6881 ± 232 kJ/d E2 + P: 6238 ± 173 kJ/d	n.s. (within group) n.s. (within group)	n.s. (within group), adj. for FFM n.s. (within group), adj. for FFM	No effect of E2 or E2 + P on REE.
	Postmenop. women of 70–80 years, before and after initiation of MHT	First month of MHT: E2 50 μg/d transdermal patch; second month of MHT: E2 50 μg/d transdermal patch + vaginal progesterone 200 mg/d for the final 7 d	IC. No further details on the calc. of REE pre-treatment, after 1 and 2 months of treatment.	6054 ± 197 kJ/d	E2: 5994 ± 266 kJ/d E2 + P: 6023 ± 166 kJ/d	n.s. (within group) n.s. (within group)	n.s. (within group), adj. for FFM n.s. (within group), adj. for FFM	

TABLE 2 (Continued)

Author, year of publication, journal	Groups of interest	Interventions/ medication details	Method, timing, and way of REE measurements	REE baseline/pre-treatment (mean ± SD)	REE post-treatment (mean ± SD)	*p*-value (ΔREE), unadjusted	*p*-value (ΔREE), adjusted	Outcome of interest: ΔREE
Kimm et al., 2001, Am J Epidemiol	Hormonal contraception users	Hormonal contraception use in general, incl. all active pharmaceutical substances, dosages, regimens, and forms of administration, incl. progestin-only contraceptives	IC. Calc. of baseline REE from the av. of 2 meas's. of REE with an interval of 10–14 d between each meas.	-	-	$p = 0.07$ (between groups)	-	
Hormonal contraception users vs. hormonal contraception non-users: +46 kcal/d; $p = 0.07$	Δ hormonal contraception non-users	-	IC. Calc. of baseline REE from the av. of 2 meas's. of REE with an interval of 10–14 d between each meas.	-	-			
Piers et al., 1997, Eur J Clin Nutr	OC users	OCs used: either phasic or constant dose comb. OCs. The most common phasic dose pill used was a comb. of EE (30–50 μg/d) + LNG (50–125 μg/d). The most common constant dose pill was EE (50 μg/d) + LNG (125 μg/d). Other comb. included EE (30 μg/d) + DSG (150 μg/d); EE (30 μg/d) + LNG (150 μg/d); and EE (35 μg/d) + NET (500 μg/d). OC use for ≥6 months.	IC. No further details on the calc. of baseline REE.	5725 ± 485 kJ/d; 5748 kJ/d (adj. for body weight); 5735 kJ/d (adj. for FFM and FM)	-	-	$p = 0.014$ (between groups), adj. for body weight $p = 0.024$ (between groups), adj. for FFM and FM	Δ OC users vs. OC non-users, adj. for body weight: +32 kcal/d ≙ +2.4%; $p = 0.014$ Δ OC users vs. OC non-users, adj. for FM and FFM: +37 kcal/d ≙ +2.8%; $p = 0.024$

(Continues)

TABLE 2 (Continued)

Author, year of publication, journal	Groups of interest	Interventions/ medication details	Method, timing, and way of REE measurements	REE baseline/pre-treatment (mean ± SD)	REE post-treatment (mean ± SD)	*p*-value (ΔREE), unadjusted	*p*-value (ΔREE), adjusted	Outcome of interest: ΔREE
	OC non-users	-	IC. No further details on the calc. of baseline REE.	5590 ± 530 kJ/d 5569 kJ/d (adj. for body weight) 5580 kJ/d (adj. for FFM and FM)	-			
Eck et al., 1997, Eur J Clin Nutr	OC users	OCs used: comb. triphasic OCs; 28 d regimen: constant EE 35 μg/d for 21 d; trilevel adjustment of progestin (NET 0.5 mg d1–d7, 0.75 mg d8–d14, 1.0 mg d15–d21); placebo pills d22–d28; OC use for ≥6 months	IC. Meas. of baseline REE 4 times within one OC cycle: during menstruation (d2, 3 or 4), in the first half (d 7, 8 or 9), in the middle (d 14, 15 or 16) and in the second half (d 22, 23 or 24) of the OC cycle.	Menstruation: 6.0 ± 0.7 MJ/d Follicular phase: 6.0 ± 0.9 MJ/d Ovulation: 5.8 ± 0.7 MJ/d Luteal phase: 6.1 ± 0.7 MJ/d	-	n.s. (within group and between groups)	n.s. (adj. for age)	Δ OC users vs. OC non-users, unadj. during: - menstruation: +24 kcal/d ≙ +1.7%; n.s. - follicular phase: +96 kcal/d ≙ +7.1%; n.s. - ovulation: −48 kcal/d ≙ −3.3%; n.s. - luteal phase: −24 kcal/d ≙ −1.6%; n.s.
	OC non-users	-	IC. Meas. of baseline REE 4 times within one menstrual cycle: during menstruation (d 2, 3 or 4), during follicular phase (d 7, 8 or 9), around ovulation (within 48 h after a positive ovulation test), and during luteal phase (d 22, 23, or 24).	Menstruation: 5.9 ± 0.7 MJ/d Follicular phase: 5.6 ± 0.5 MJ/d Ovulation: 6.0 ± 0.5 MJ/d Luteal phase: 6.2 ± 0.9 MJ/d		n.s. (within group and between groups)	n.s. (adj. for age)	
Diffey et al., 1997, Br J Nutr	OC users	OCs used: comb. OCs: The most used phasic-dose OC was a comb. of EE (30–50 μg/d) + LNG (50–125 μg/d). The most used constant dose OC was EE (50 μg/d) + LNG	IC. No further details on the calc. of baseline REE.	5841 ± 471 kJ/d	-	n.s.	$p = 0.001$ (between groups), adj. for body weight $p = 0.002$ (between groups), adj. for FM and FFM	Δ OC users vs. OC never-users, unadj.: +208 kcal/d ≙ +3.7%, n.s. Δ OC users vs. OC never-users, adj. for body weight: +4.9%; $p = 0.001$ Δ OC users vs. OC never-users, adj. for

TABLE 2 (Continued)

Author, year of publication, journal	Groups of interest	Interventions/ medication details	Method, timing, and way of REE measurements	REE baseline/pre-treatment (mean ± SD)	REE post-treatment (mean ± SD)	*p*-value (ΔREE), unadjusted	*p*-value (ΔREE), adjusted	Outcome of interest: ΔREE
		(125 μg/d). Other comb. included EE (30 μg/d) + DSG (150 μg/d); EE (30 μg/d) + LNG (150 μg/d); and EE (35 μg/d) + NET (500 μg/d). OC use for ≥6 months.						FM and FFM: +4.8%; $p = 0.002$
	OC never-users	-		5633 ± 614 kJ/d	-			

Abbreviations: av., average; calc., calculation; CEE, conjugated equine estrogens; d, day/days; comb., combined/combinations; DSG, desogestrel; E2, estradiol; EE, ethinyl estradiol; FFM, fat-free mass; FM, fat mass; GnRH-Ag, gonadotropin-releasing hormone agonist; IC, indirect calorimetry; i.m., intramuscular; LNG, levonorgestrel; meas., measurement; MHT, menopausal hormone therapy; MPA, medroxyprogesteroneacetate; NET, norethisterone; OC, oral contraceptive; REE, resting energy expenditure.

estrogen used was either estradiol (E2) or conjugated equine estrogens (CEE), in the context of MHT,[147,148,153,155] or ethinyl estradiol (EE), in the context of contraception.[146,149–152,154] E2 dose and type of application in MHT varied from 50 to 75 μg/d transdermally[147,153] to no further specification.[155] CEE dose and mode of application in MHT varied from 0.625 mg/d orally[148] to no further information.[155] EE dose and form of application in contraception varied from 20 to 50 mcg/d orally[146,149–151,154] to a generalized statement of inclusion of all HC methods, and thus also of progestin-only methods.[152] The type of progestin used in MHT varied between medroxyprogesterone acetate (MPA),[148,153] progesterone,[147] and no further details regarding the used progestin.[155] Two of the four MHT studies did not specifically distinguish between sequential and continuous-combined use of the progestin,[148,155] whereas the other two studies reported sequential use.[147,153] The progestins in the context of HC were levonorgestrel,[149,154] desogestrel,[149,154] and norethisterone,[146,149,154] or there was no more specific information about this detail.[150–152] The mean age of the subjects enrolled in the study groups of interest in the six contraceptive trials ranged between 19[152] and 26[149] years, and that of the subjects in the four MHT studies ranged between 33[153] and 72[147] years. The subjects in the contraceptive studies had an average BMI of 20.8[146] to 27.8[152] kg/m^2, and those in the MHT studies had a BMI of 22.9[155] to 27.3[153] kg/m^2. To measure REE, the indirect calorimetry method was consistently used in all included studies.[146–155] In all six contraceptive studies as well as in two of the MHT studies, between-group differences in REE were reported (HC users versus non-users or MHT users versus non-users). Within-group differences in REE before and after starting HC or MHT were not investigated.[146,148–152,154,155] Only the MHT studies by Melanson et al. and Anderson et al. also reported within-group differences at pre-MHT[147,153] and 1,[147] 2,[147] and 5[153] months after MHT initiation.

3.2 | Impact of estrogens on resting energy expenditure

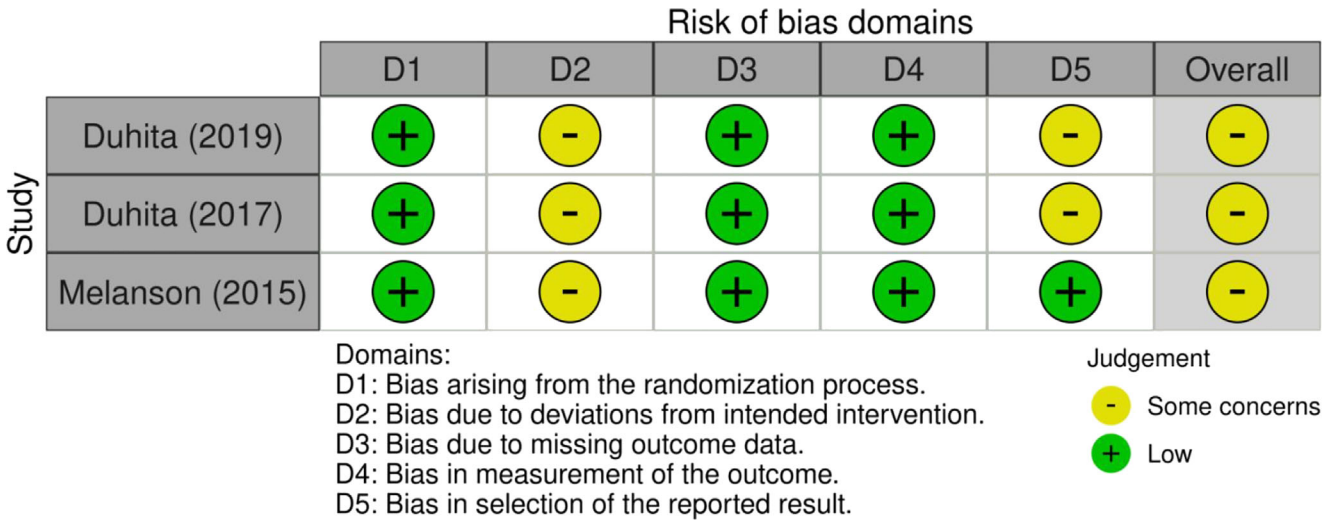
Regarding the six studies on contraceptives,[146,149–152,154] the picture that clearly emerges is that the various HC methods exert a neutral influence on REE or may even slightly increase it. Thus, in the cross-sectional study by Piers et al., the measured REE of women on combined oral contraceptives (OCs) adjusted for body weight was significantly higher than that of women not on combined OCs by 2.4% and +32 kcal/d ($p = 0.014$), respectively. REE adjusted for fat mass (FM) and fat-free mass (FFM), two major confounders of REE, was also significantly higher in women taking combined OCs as compared with women not taking combined OCs, by 2.8% corresponding to +37 kcal/d ($p = 0.024$).[154] In the study by Diffey et al., the REE-enhancing effect of combined OCs was even more pronounced. Although the raw (unadjusted) results showed a 3.7% increase in REE, equivalent to +208 kcal/d in combined OC users compared with combined OC never-users, the difference was not significant. However, after applying an analysis of covariance with either body weight or a combination of FM and FFM as covariates, the differences between

TABLE 3 Risk of bias assessment of non-randomized trials according to the quality assessment tool by Thomas H.

Study name	A	B	C	D	E	F	Global judgment
Aubertin (2008)	Strong	Moderate	Weak	Moderate	Strong	Strong	*Moderate*
Reimer (2005)	Moderate	Weak	Moderate	Moderate	Strong	Strong	*Moderate*
Anderson (2001)	Moderate	Moderate	Moderate	Moderate	Strong	Weak	*Moderate*
Kimm (2001)	Strong	Weak	Moderate	Moderate	Strong	Strong	*Moderate*
Piers (1997)	Moderate	Weak	Moderate	Moderate	Strong	Strong	*Moderate*
Eck (1997)	Strong	Moderate	Moderate	Moderate	Strong	Strong	*Strong*
Diffey (1997)	Moderate	Weak	Moderate	Moderate	Strong	Strong	*Moderate*

Note: A, selection bias; B, study design; C, confounders; D, blinding; E, data collection methods; F, withdrawals and dropouts. Thomas H. Quality assessment tool for quantitative studies. Effective Public Health Practice Project. McMaster University, Toronto. Recommended by *Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7* (27):*iii-x, 1–173. doi*: 10.3310/hta7270. *PMID: 14499048*.

TABLE 4 Risk of bias assessment of randomized controlled trials according to the Cochrane Risk of Bias 2 (RoB 2) tool.



Note: McGuinness, LA, Higgins, JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1–7. https://doi.org/10.1002/jrsm.1411.

groups were found significant. Accordingly, combined OC users had a significantly higher REE than combined OC never-users, 4.9% ($p = 0.001$) and 4.8% ($p = 0.002$), respectively.[149] In the remaining four contraceptive studies, no significant effect of HC use on REE was found. Nevertheless, the cross-sectional study by Kimm et al. found a clear trend toward an increase in REE by +46 kcal/d ($p = 0.07$) with contraceptive medication use.[152] In the cross-sectional study by Eck et al., examining the effect of combined OC use on energy balance and its components across the different phases of the menstrual cycle, no significant differences in REE were found among the different phases of the menstrual cycle itself, nor between the groups of combined OC users and non-users. Combined OC users had a higher REE than non-users during menstruation (+24 kcal/d ≙ 1.7%) and during the follicular phase (+96 kcal/d ≙ 7.1%), when endogenous estradiol levels are physiologically low, whereas REE was lower during ovulation (−48 kcal/d ≙ 3.3%) and the luteal phase (−24/d kcal ≙ 1.6%), when endogenous estradiol levels are physiologically high. This observation again speaks for the influence of sex steroids on the REE. However, as noted above, all differences showed no statistical significance.[146] Likewise, the two RCTs by Duhita et al. with a very small number of subjects did not describe any significant effect of the use of combined OCs on REE either.[150,151] At least, none of the contraceptive studies showed a significant negative effect of HC use on REE.

The four MHT studies[147,148,153,155] show a similar picture. In the RCT by Melanson et al., in which young healthy women received ovarian function suppression with GnRH analogs with or without add-back therapy, a significant decrease in REE was observed in the GnRH-Ag + placebo substitution group (3.7%, corresponding to −54 kcal/d, $p \leq 0.05$), an effect not observed in the GnRH-Ag + E2 substitution group (+6 kcal/d). Although REE did not differ significantly between groups before the intervention, it did after the intervention (difference in between-group changes: 60 kcal/d, $p < 0.05$). Pharmacological suppression of sex hormones and thus iatrogenically induced menopause reduced REE. E2 add-back therapy not only attenuated the decrease in REE but completely counteracted this effect.[153] In the cross-sectional study by Aubertin-Leheudre et al., the

REE of actual MHT users was compared with that of MHT never-users. The physiologically postmenopausal women of both groups did not differ in baseline characteristics such as age, BMI, or body composition (FM and FFM), but MHT users had a significantly higher REE than MHT non-users ($\Delta + 222$ kcal/d; $p = 0.038$). The magnitude of the increase in REE due to MHT use corresponded to a large and significant Cohen's effect size of 0.78.[148] A clear trend in REE pattern, although not statistically significant, was evident in the cross-sectional study with a very small number of cases by Reimer et al. comparing the REE of postmenopausal actual MHT users with that of MHT non-users. Thus, the REE was highest in the luteal phase of premenopausal women, followed by that of the follicular phase of premenopausal women, the REE of postmenopausal women using MHT, and finally that of postmenopausal women not using MHT. The REE was significantly lower ($p < 0.05$) in postmenopausal women not taking MHT compared with premenopausal women, but not in women taking MHT.[155] In the prospective cohort study by Anderson et al., REE was examined in younger (45–55 years) and older (70–80 years) subjects before and after initiation of MHT. No significant effect of short-term (1 and 2 months) E2 or E2 + progesterone administration on REE was found, even when adjusted for FFM.[147] In summary, estrogen substitution in the context of MHT resulted in a significant increase in REE in two of the four studies,[148,153] whereas it showed a distinct, but nonsignificant trend toward an increase in REE in one[155] and a neutral effect in another study.[147] As in the studies on contraception, no single study could be identified in which estrogen substitution led to a significant decrease in REE.

4 | DISCUSSION

4.1 | Strengths and limitations

It should be noted that only two[147,153] of all included studies comprehensibly investigated estrogen effects exclusively, without any possible confounding by the concomitant use of a progestin. Thus, the RCT by Melanson et al.[153] showing a significant positive effect and the prospective cohort study by Anderson et al.[147] observing no significant effect of estrogen administration on REE provide the most valid evidence regarding our research question.

It is also worth mentioning that in the contraceptive studies, the timing of the REE measurement during the menstrual cycle is of great importance in the control group, in contrast to the MHT studies with the consistently postmenopausal patients. It is striking that the two studies by Piers et al.[154] and Diffey et al.[149] reported a significant increase in REE with OC use but did not mention the timing of the REE measurement during the menstrual cycle of OC non-users. Assuming that the REE measurement in these two studies took place only during the early follicular phase in OC nonusers, the effect of estrogens on REE over the entire course of the menstrual cycle would not be accurately represented by a single measurement, given the drastic physiological fluctuations of sex steroids in the menstrual cycle. REE measurements in the follicular phase may underestimate REE over the course of a menstrual cycle, and measurements in the luteal phase may overestimate it. Here, Eck et al.[146] clearly showed that the REE of OC non-users was lower in the first cycle phase than that of OC users. In the second half of the menstrual cycle, however, the exact opposite was the case. The timing of the REE measurement in the menstrual cycle is therefore of great importance. The average influence of sex steroids across the cycle of HC nonusers is better represented in the work of Duhita et al.[150] and Kimm et al.[152] by calculating the average REE from multiple measurements across the menstrual cycle, with REE measurements evenly distributed between the follicular and luteal phases. In contrast, Eck et al.[146] evaluated the REE measurements in the follicular phase, at the time of ovulation, in the luteal phase, and during menstruation separately and then compared them between OC users and OC non-users.

Furthermore, it should be critically noted that in exactly those two[149,154] of the six[146,149–152,154] HC papers that showed a significant positive influence of estrogens on REE, high-dose OCs with up to 50 μg EE/d were used. Because these are EE dosages as they are no longer standardly used nowadays, the results cannot be uncritically extrapolated to the OCs currently in use.

Another limitation of our review and a potential reason that some studies failed to demonstrate an effect of estrogen medication on REE could be the fact of underpowerment. If the included studies are subdivided according to the number of subjects of interest, a significant estrogen use-dependent increase in REE (Piers et al. with 89 subjects,[154] Diffey et al. with 46 subjects,[149] and Melanson et al. with 45 subjects[153]) and a nonsignificant but undeniable tendency in the same direction (Kimm et al. with 147 subjects[152]) can be observed in four[149,152–154] of the five[147,149,152–154] studies with the largest sample size. However, with the exception of one (Aubertin-Leheudre et al. with 26 participants[148]) of the five studies with the smallest number of participants, there was no effect of estrogen use on REE (Eck et al. with 32 subjects, Duhita et al. with 16 subjects,[150] Duhita et al. with 14 subjects,[151] and Reimer et al. with 13 subjects[155]).

One of the greatest weaknesses of our systematic review, which limits the significance of its results, is not at least the insufficient availability of high-quality studies on our specific research question.

One of the strengths of our systematic review is the comprehensive literature search, covering not only estrogens but all sex steroids, to identify all relevant studies on this topic and to ensure that the available evidence is presented as fully as possible. We also restricted inclusion to normal-weight and overweight women to exclude confounding factors such as metabolic adjustments and hormonal alterations that typically occur when women are obese or underweight. As is typical for systematic reviews in general, our article is characterized by an objective methodology that ensures transparency and reproducibility. By summarizing the evidence from several individual studies in this article, it is possible to make a comprehensive statement about the likely effect of estrogens on REE. This should help to draw clear conclusions and provide the basis for decisions concerning a much-discussed topic in daily practice.

In summary, our results support an REE-enhancing effect of estrogen administration in the context of HC or MHT. However, overall scientific evidence on the impact of estrogen administration on REE is limited, and the quality of available evidence is low to moderate.

4.2 | Discussion of the results with regard to the influence of estrogens on BAT

Despite the positive aspects of HC and/or MHT, the fear of unwanted weight gain is one of the main reasons for women not to initiate or to early discontinue these therapies.[7–11] For clinicians, easing women's anxiety is difficult regarding the currently limited understanding of the effects of sex hormones on body weight regulation. Given that a low REE is a confirmed predictive factor for weight gain[156] and consecutively for the development of obesity, research into the influence of sex steroids on REE is a particularly exciting area. Considering the balance of evidence, our data suggest a favorable effect of circulating estrogen levels and estrogen administration in the form of HC and MHT on REE.

Studies have shown that hormonal fluctuations during the menstrual cycle influence REE.[102–108] According to our data, suppression of these fluctuations by HC seems to have neutral or even positive effects on body weight regulation in terms of an increase in REE.

Regarding the influence of MHT on weight development in perimenopause and postmenopause, it should be pointed out that the weight gain associated with perimenopause and postmenopause is rather a consequence of the age-related tendency to reduced physical activity, the associated loss of muscle mass, and the overall reduced energy requirement.[157] Contrary to mainstream belief, MHT actually counteracts this age-related tendency to gain weight, with one of the mechanisms being an increase in REE.

The estrogenic effect on BAT activity may be the underlying reason for this observation. Indeed, considering the magnitude of the estrogen-associated increase in REE (ranging from no effect[146,147,150–152,155] to +32 kcal/d,[154] +37 kcal/d,[154] +60 kcal/d,[153] +208 kcal/d,[149] and +222 kcal/d[148]), this corresponds to the additional energy expenditure associated with activation of BAT thermogenesis. It is estimated that BAT-specific energy expenditure can account for up to 2.5%–8% of REE.[36,48,158] The limited data available on this issue quantify the actual contribution of BAT thermogenesis to TEE at 7 kcal/d in thermoneutral environments to approximately 200 kcal/d in mild cold exposure.[158–161] This rather small contribution of BAT to TEE is mainly due to its low overall tissue mass of about 50–500 g[162] rather than its metabolic activity, which is still several times higher compared with other tissues of the human body.[161]

As mentioned at the very beginning, the development of obesity is the consequence of a chronic disturbance of energy homeostasis with a persistent positive energy balance. The average weight gain underlying obesity, which usually commences in young adulthood, is 0.5–0.7 kg per year. This corresponds to a daily positive energy balance of just 12–17 kcal/day at an average energy density of 8840 kcal per kg body weight and lies thus within the range of the BAT-specific contribution to TEE[161,163] and estrogen-mediated activation of BAT thermogenesis, respectively. Hence, the contribution of BAT to REE may be small but not negligible. It seems that low but sustained activity of BAT thermogenesis may significantly counteract the development of obesity. However, current estimates of BAT thermogenesis capacity are at the low end of what would potentially be clinically possible through its chronic stimulation by various endogenous or exogenous factors.[161] It has been shown that the metabolic activity of BAT can be increased many-fold as well as BAT mass can be newly formed and existing depots can be significantly enlarged even in adulthood by long-term cold exposure or cold acclimatization[159,161,164,165] and catecholamine-secreting tumors such as pheochromocytomas and paragangliomas.[76,166,167] According to our results, estrogen administration could have a similar effect, although to a lesser extent. The assumption that estrogen-mediated activation of BAT thermogenesis underlies the estrogen-induced increase in REE is reasonable, although the exact mechanisms of the estrogen-induced REE increase cannot be elucidated with this systematic review. Future research needs to focus more on the metabolic effects of sex steroid administration.

Finally, it should be emphasized that estrogens have an anorexigenic effect and thus prevent increased EI from compensating for increased REE.[168] Together with this fact, our results suggest that the energy balance changes in a negative direction under the influence of estrogens. Thus, the widespread fear of weight gain solely as a result of taking HC or MHT is therefore unsubstantiated. This article is intended to help clinicians educate women accordingly and alleviate their fears in this regard.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest statement.

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