

Linking Physical Activity to Breast Cancer via Sex Hormones, Part 1: The Effect of Physical Activity on Sex Steroid Hormones



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ABSTRACT

The effect of physical activity on breast cancer risk may be partly mediated by sex steroid hormones. This review synthesized and appraised the evidence for an effect of physical activity on sex steroid hormones. Systematic searches were performed using MEDLINE (Ovid), EMBASE (Ovid), and SPORTDiscus to identify experimental studies and prospective cohort studies that examined physical activity and estrogens, progestins, and/or androgens, as well as sex hormone binding globulin (SHBG) and glucocorticoids in pre- and postmenopausal women. Meta-analyses were performed to generate effect estimates. Risk of bias was assessed, and the GRADE system was used to appraise quality of the

evidence. Twenty-eight randomized controlled trials (RCT), 81 nonrandomized interventions, and six observational studies were included. Estrogens, progesterone, and androgens mostly decreased, and SHBG increased, in response to physical activity. Effect sizes were small, and evidence quality was graded moderate or high for each outcome. Reductions in select sex steroid hormones following exercise supports the biological plausibility of the first part of the physical activity–sex hormone–breast cancer pathway. The confirmed effect of physical activity on decreasing circulating sex steroid hormones supports its causal role in preventing breast cancer.

See related reviews by Lynch et al., p. 11 and Drummond et al., p. 28

Introduction

There is strong evidence that women who accrue higher levels of physical activity may have a reduced risk of developing breast cancer compared with their less active counterparts (1). Despite this, the causal nature of this relationship remains unclear, limiting the certainty with which physical activity can be promoted as a means to reduce breast cancer risk (2). An improved understanding of the

mechanistic pathways that may underlie the physical activity–breast cancer relationship will strengthen causal inference.

Sex steroid hormones have been proposed as a key mechanistic pathway underlying the association between higher physical activity and reduced breast cancer risk (3–5). Higher levels of physical activity have, in some instances, been associated with lower levels of circulating sex hormones in both pre- and postmenopausal women (6, 7). In premenopausal women, regular, vigorous-intensity exercise may disrupt menstrual function, and potentially delay the onset of menarche (8–10). Regular physical activity attenuates age-associated weight gain (11), which in turn may reduce levels of circulating estrogens and androgens (12). Breast cancer is widely acknowledged to be a hormone-dependent disease (13). Higher levels of estrogens, progesterone, and androgens, as well as lower levels of sex hormone binding globulin (SHBG) have been implicated in the development of breast cancer (13–15). This could partially explain the link between higher physical activity and reduced breast cancer risk. However, most published reviews relating to the physical activity–sex hormone–breast cancer pathway have been narrative reviews. There is a strong need for systematic review, synthesis of data (including meta-analysis, where possible) and study quality appraisal to conclude that this pathway is a causal contributor to the physical activity–breast cancer association.

The current research utilizes a causal evidence synthesis framework developed by the World Cancer Research Fund (WCRF) International and University of Bristol to review evidence for a physical activity–sex hormone–breast cancer pathway (16). In our protocol article (2), we detailed the initial stage of this process, which used TeMMPo (17), a novel text mining platform, to prioritize sex steroid hormone mediators that may underlie physical activity–breast cancer associations, based on the quantity of evidence for each mediator. In this review, we aim to synthesize and appraise the evidence for an effect of physical activity on each of these sex hormones. The review of the evidence for

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the latter step assessing the putative pathway of interest is published concurrently (18).

Materials and Methods

The methods for this review have been outlined, in detail, in our protocol article (2), registered on PROSPERO (CRD42020146736) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (19). In brief, systematic searches of MEDLINE (Ovid), EMBASE (Ovid), and SPORTDiscus were completed by 30 August 2019. The search terminology is presented in the Supplementary Material (Supplementary Table ST1). Peer-reviewed, experimental studies and prospective cohort studies were included if they examined the effect of physical activity on sex hormones in apparently healthy (i.e., free of a medical diagnosis for a condition that may alter how sex hormones respond to exercise), post-menarche females. Outcomes were estrogens, progesterone, androgens, sex hormone binding globulin (SHBG), and glucocorticoids, which were identified as potential mediators of the physical activity–breast cancer relationship by TeMMPo (2). Following duplicate removal, two reviewers independently screened the titles and abstracts, and then the full texts, and studies that were not relevant were excluded. The Cochrane Collaboration Tool, ROBINS-I, and ROBINS-E were used to assess risk of bias in randomized controlled trials (RCT), nonrandomized interventions, and observational studies, respectively (20–22). To rate the overall quality of evidence and the strength of any findings generated, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used (23). For all outcomes, extracted data were summarized and presented descriptively. Where study design, exposures, outcomes, and analyses were defined consistently in at least three separate RCTs, random-effects meta-analysis was used to generate an effect estimate [standardized mean difference (SMD) 95% confidence interval (CI)]. All statistical analyses were performed using Stata version 16 (Stata Corporation, College Station, Texas).

Results

Search results

Results of the searches are presented in Fig. 1. Of 11,573 results returned across all five database search sets, there were 114 studies (127 publications) that assessed the effect of physical activity or exercise on sex steroid hormones or SHBG. These included 28 RCTs (24–57), 81 nonrandomized interventions (58–145), and six observational studies (6, 7, 146–149). The pre-post studies included 30 that examined the acute effects of exercise (58–110) and 51 that examined the effects of more than a single exercise session on sex steroid hormones (111–145).

Study characteristics

Study characteristics are presented in Supplementary Methods and Material (Supplementary Tables S2A–S2D). There were nine RCTs that included premenopausal (24–37), 18 RCTs that included postmenopausal (38–56), and one that included perimenopausal (57) women. Sample sizes ranged from 18 to 391 in studies of premenopausal, and from 16 to 382 in studies of postmenopausal women. The intervention consisted of predominantly aerobic exercise in 14 studies (25–27, 31, 32, 34–36, 38, 40, 44, 46, 49, 50), strength training in six (29, 30, 41, 54–56), a combination of aerobic and strength in seven (24, 39, 42, 47, 52, 53, 57), and yoga in one (48), with an intervention duration ranging from 8 weeks to 12 months. An inactive control group served as the comparator in 21 studies (24–26, 29–32,

34–36, 39, 40, 42, 46–49, 53–57). Four studies offered stretch, flexibility, or group information classes during the intervention period (38, 41, 50, 52). Three studies had a different exercise intensity or dose as a comparator (27, 28, 44). Outcomes included circulating SHBG ($n = 9$; refs. 24, 25, 34, 44, 46, 49, 52, 53), estradiol ($n = 15$; refs. 26, 27, 34, 35, 40–42, 44, 46, 50, 53, 55–57), estrone ($n = 6$; refs. 40, 42, 44, 46, 50, 53), estrogen ($n = 5$; refs. 30–32, 36, 47), free estradiol ($n = 6$; refs. 34, 40, 44, 46, 50, 53), estrone sulfate ($n = 2$; refs. 34, 53), bioavailable estradiol ($n = 1$; ref. 34), 2-OH-E1 ($n = 3$; refs. 25, 33, 38), 16 α -OH-E1 ($n = 3$; refs. 25, 33, 38), progesterone ($n = 5$; refs. 32, 34, 48, 56, 57), androstenedione ($n = 5$; refs. 40, 42, 46, 51, 53), testosterone ($n = 14$; refs. 24, 27, 29, 34, 40, 41, 46, 51–55, 57), free or bioavailable testosterone ($n = 5$; refs. 34, 40, 46, 51, 53), dehydroepiandrosterone (DHEA, $n = 3$; refs. 51, 53, 57), dehydroepiandrosterone sulfate (DHEAS, $n = 4$; refs. 51, 53, 54, 57), and cortisol ($n = 7$; refs. 24, 29, 37, 39, 42, 52, 55). In studies of premenopausal women, steroid hormone levels were assessed in the follicular ($n = 5$; refs. 26, 29–31, 34), luteal ($n = 1$; ref. 25), or both ($n = 3$) phases of the menstrual cycle.

Nonrandomized interventions included studies that examined acute hormonal responses to a single exercise session ($n = 51$; refs. 58–110), or multiple exercise sessions ($n = 30$; refs. 111–145), with interventions ranging from 5 days to 6 months. Samples included premenopausal women only (acute $n = 43$, multiple sessions $n = 17$), postmenopausal women only (acute $n = 4$, multiple sessions $n = 9$), or both pre- and postmenopausal women (acute $n = 4$, multiple sessions $n = 4$). Sample sizes ranged from $n = 5$ to $n = 75$ in acute exercise interventions, and $n = 6$ to $n = 148$ in interventions of a longer duration. Exercise interventions included aerobic exercise (acute $n = 32$, multiple sessions $n = 18$), anaerobic exercise (acute = 1) strength exercise (acute $n = 15$, multiple sessions $n = 8$), and combined aerobic and strength training (acute $n = 3$, multiple sessions $n = 4$). Twenty-eight studies had a relevant comparison condition, which included menstrual cycle phase (acute $n = 8$), participant menopause status (acute $n = 3$, multiple sessions $n = 3$), participant fitness or body composition (acute $n = 4$, multiple sessions $n = 1$), exercise type or dose (acute $n = 6$, multiple sessions $n = 1$), or time of day of exercise (acute $n = 3$). Outcomes included SHBG (acute $n = 2$, multiple sessions $n = 14$), estradiol (acute $n = 25$, multiple sessions $n = 15$), estrone (multiple sessions $n = 4$), estrogen (acute $n = 2$, multiple sessions $n = 3$), progesterone (acute = 14, multiple sessions = 12), testosterone (acute = 19, multiple sessions = 13), free testosterone (acute = 5, multiple sessions = 2), androstenedione (acute = 2, multiple sessions = 2), DHEA (acute = 3), DHEAS (acute = 3, multiple sessions = 1), and cortisol (acute = 26, multiple sessions = 4).

Prospective cohort studies included pre- ($n = 3$; refs. 7, 146, 149) and post- ($n = 3$; refs. 6, 147, 148) menopausal women and had sample sizes ranging from $n = 104$ to $n = 623$ participants. Each used self-reported measures of physical activity, with follow-up duration ranging from one or two menstrual cycles to four years. Outcomes included SHBG ($n = 2$; refs. 6, 148), estradiol ($n = 5$; refs. 6, 7, 146–148), estrone ($n = 3$; refs. 6, 147, 148), free estradiol ($n = 2$; refs. 6, 148), bioavailable estradiol ($n = 2$; refs. 6, 148), estrone sulfate ($n = 1$; ref. 6), progesterone ($n = 1$; ref. 146), testosterone ($n = 4$; refs. 6, 147–149), androstenedione ($n = 3$; refs. 6, 147, 148), DHEA ($n = 1$; ref. 6), and DHEAS ($n = 1$; ref. 6).

Risk of bias

Risk of bias results are presented in Supplementary Materials and Methods (Supplementary Tables S3A–S3D). Sources of bias in RCTs included performance bias (all RCTs), due to the inability to blind

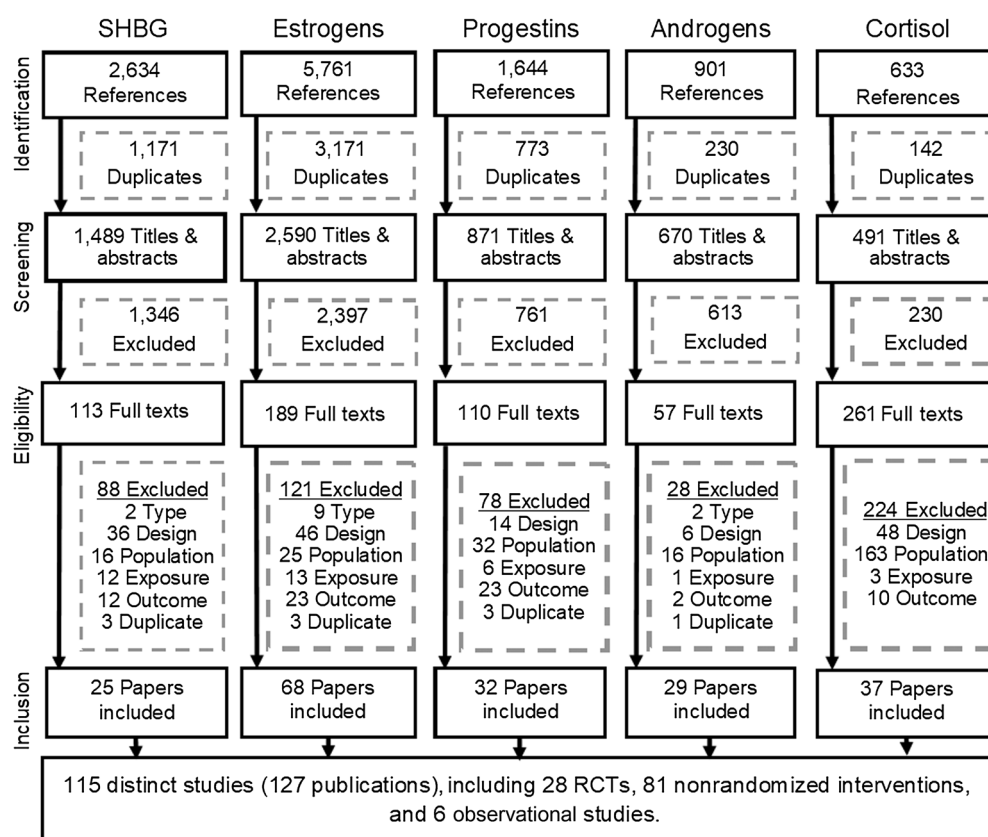


Figure 1.
PRISMA flow diagram of literature search, screening, and study selection.

participants to the fact they are completing exercise, as well as attrition bias, with 12 studies having greater than 10% attrition or noncompliance (25, 27, 32, 34, 35, 39, 42, 48, 54, 57). There was insufficient information regarding selection bias in 19 studies (24, 26, 27, 29–31, 34–36, 39, 41, 42, 47, 49, 52–56) and insufficient information on the measurement, accuracy, reliability, or sensitivity of hormone assays in two studies (24, 39). All nonrandomized interventions had at least a moderate risk of bias owing to the presence of confounding and seven scored serious for confounding as participant body composition was not considered or reported when selecting or describing participants (58, 59, 64, 73, 79, 101, 109, 125). Studies also scored moderate for participant selection ($n = 2$; refs. 115, 117), intervention classification and the potential for intervention deviation ($n = 13$; refs. 63, 69, 71, 116, 117, 120, 121, 124, 131, 133, 138, 142, 144), outcome assessment ($n = 1$), as well as the number of outcomes reported ($n = 2$; refs. 129, 138). Five observational studies had moderate risk of bias overall, owing to the potential for confounding, self-reported assessment of physical activity, or the number of analyses performed and reported (6, 7, 146, 148, 149). One observational study had serious risk of bias as it did not adjust for important confounders and as the assessment of estradiol lacked adequate sensitivity for approximately half the participants (147).

Effect of physical activity on sex hormones and SHBG

Meta-analysis results are presented in Fig. 2 (estrogens and progesterone) and Fig. 3 (androgens, SHBG, and cortisol) and in Supplementary Methods and Materials (Supplementary Figures 1–4).

Results from individual studies that were not included in meta-analyses are presented in Supplementary Methods and Materials (Supplementary Tables S4A–S4D).

SHBG

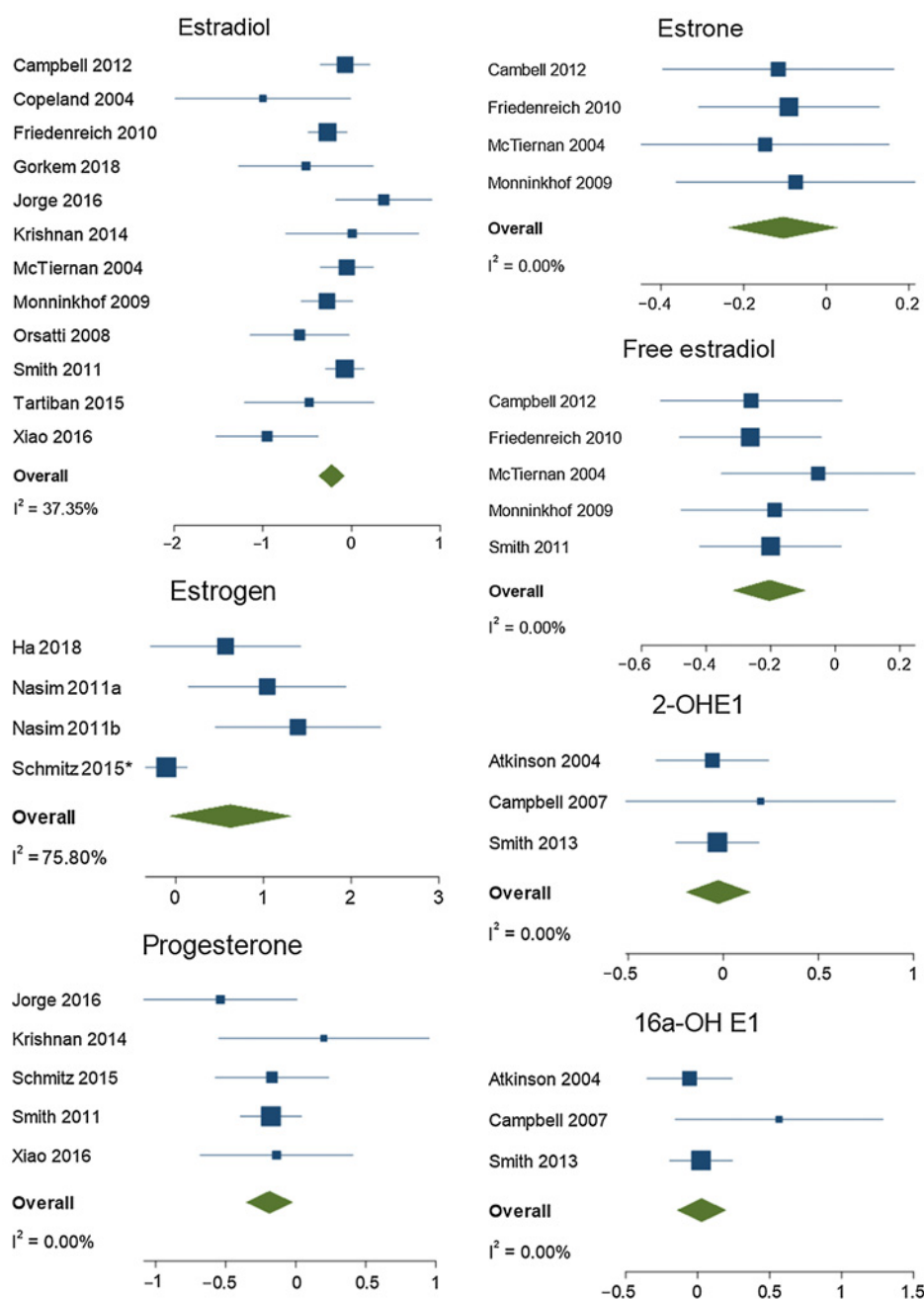
A meta-analysis of RCTs (8 studies, $n = 1,353$) identified a small increase in SHBG following exercise (SMD = 0.13; 95% CI = 0.02, 0.24; $I^2 = 0\%$). Only one individual RCT examined exercise dose and SHBG and it did not identify a clear dose–response relationship (44). Nonrandomized interventions that examined the response of SHBG to multiple exercise sessions mostly reported no significant changes from baseline (113, 115, 116, 119, 120, 127, 128, 131, 132, 137, 139, 140, 145). The acute response of SHBG to a single session of exercise was described by two studies. These observed a small increase (~10%) in SHBG at the conclusion of exercise, which returned to baseline upon recovery (73, 98). Findings from observational studies were consistent with those from the meta-analysis, with 2 of 2 studies identifying higher levels of SHBG in postmenopausal women who reported higher levels of physical activity (6, 148).

Estrogens

Meta-analyses of RCTs identified small decreases in estradiol (12 studies, $n = 1,452$; SMD = -0.22 ; 95% CI = -0.37 , -0.08 ; $I^2 = 37\%$) and free estradiol (5 studies, $n = 1,033$; SMD = -0.20 ; 95% CI = -0.32 , -0.09 ; $I^2 = 0\%$) in response to exercise. There was a suggestion of a small, but nonsignificant, decrease in estrone (4 RCTs, $n = 878$; SMD = -0.10 ; 95% CI = -0.24 , 0.03 ; $I^2 = 0\%$). There was no

Figure 2.

Abbreviated forest plots for estrogens and progesterone. The x-axis represents the SMD between exercise and control groups.



effect of exercise on estrogen or estrogen metabolites 2-OH-E1 or 16a-OH-E1 identified via meta-analysis. As moderate heterogeneity was evident in the estradiol meta-analysis, subgroup analysis was performed to identify any differences in effect according to exercise type and menopausal status. A decrease in estradiol was evident in studies that prescribed both aerobic (6 studies, $n = 1,060$; SMD = -0.15 ; 95% CI = $-0.27, -0.03$; $I^2 = 0\%$) and resistance exercise (3 studies, $n = 116$; SMD = -0.80 ; 95% CI = $-1.17, -0.43$; $I^2 = 0\%$), and in studies that enrolled only postmenopausal women (9 studies, $n = 1,070$; SMD = -0.28 ; 95% CI = $-0.49, -0.06$; $I^2 = 60\%$). There was no clear evidence of an effect identified in studies that prescribed combined training (2 studies) or yoga (1 study), or studies that included only pre- (2 studies) or peri- (1 study) menopausal

women. In individual RCTs, performing a higher quantity of moderate-activity exercise (300 minutes compared with 150 minutes per week) did not result in a greater effect on hormone levels (32, 44), nor did high-intensity interval exercise compared with continuous moderate-to-vigorous aerobic exercise (27, 28).

Of 14 nonrandomized interventions that had more than a single exercise session, seven reported a reduction in resting estradiol levels (117, 121–124, 130, 133, 143). This was more frequently detected in the luteal rather than the follicular phase of the menstrual cycle (121, 124, 130, 133). Two studies that examined differences in hormone responses between pre- and postmenopausal women did not identify an effect of exercise on sex steroid hormones (136, 141). In studies of acute exercise, estradiol appeared to increase following a

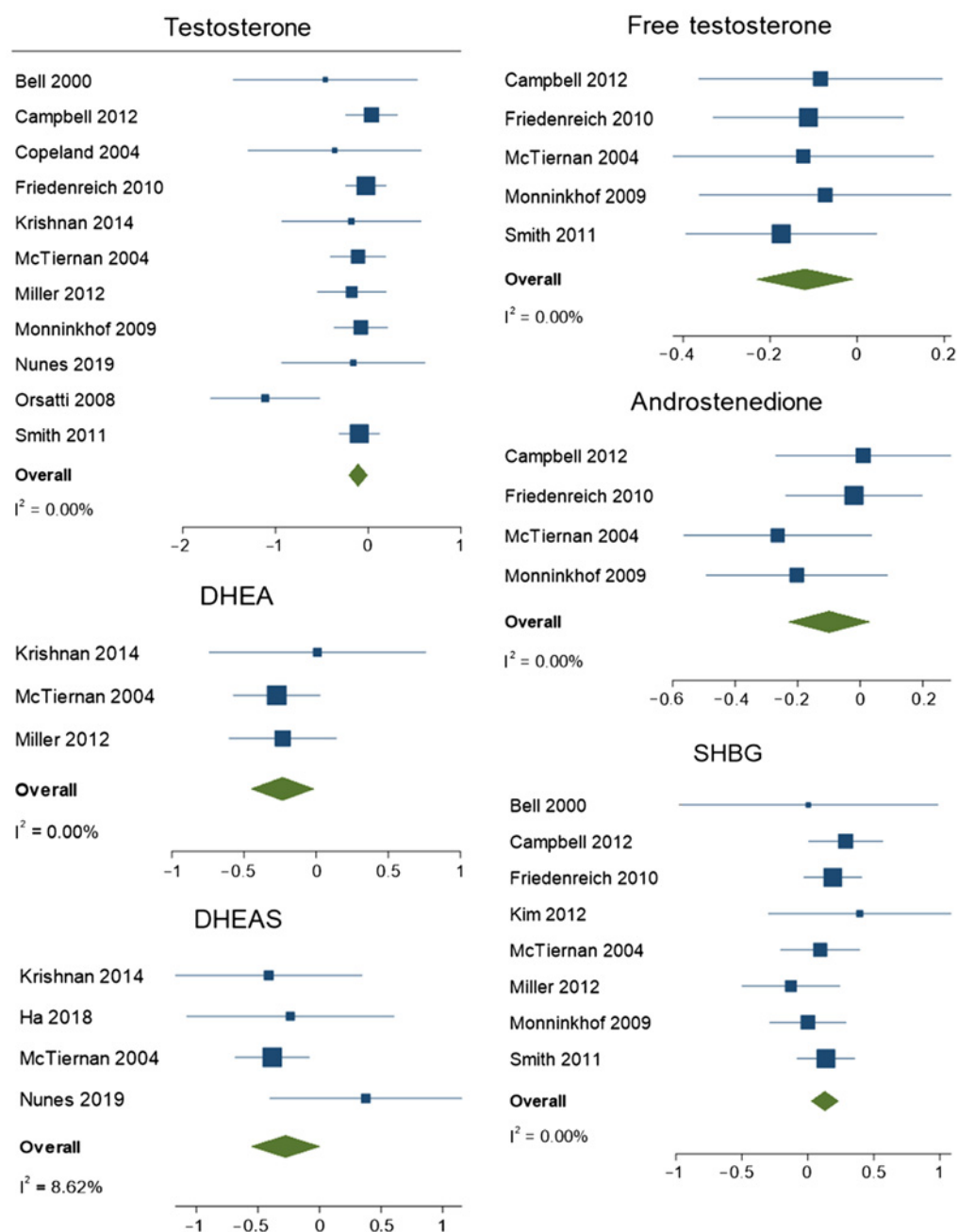


Figure 3. Abbreviated forest plots for androgens and SHBG. The x-axis represents the SMD between exercise and control groups.

single session before returning to baseline upon recovery (60–65, 67, 69–72, 75, 79, 81, 83, 84, 89, 96, 97, 107, 110). This relationship was influenced by exercise type, duration and intensity, recent exercise history, and cycle phase. Longer, more intense exercise led to greater increases in estradiol (69, 79, 83). The response was also greater following a week of intense training (75) and greater in the luteal phase of the menstrual cycle (60–63, 68, 81, 89, 94, 96, 97). Although there was no difference between pre- and postmenopausal women in acute responses to prolonged endurance exercise (a 50–100 km run;

ref. 71), acute changes in estradiol levels were more evident in premenopausal women following strength training (72, 104).

In prospective cohort studies, more physical activity was associated with less estradiol in 1 of 2 studies of premenopausal women and in 1 of 3 studies in postmenopausal women (6, 7, 146–148). Consistent with the meta-analysis results, higher levels of physical activity were associated with less bioavailable estradiol and free estradiol in 2 of 2 studies of postmenopausal women (6, 148). No association between physical activity and estrone levels were identified (6, 147, 148).

Progesterone

In RCTs, progesterone levels decreased in response to exercise (5 studies, $n = 548$; SMD = -0.19 ; 95% CI = $-0.36, -0.02$; $I^2 = 0\%$). Only 2 of 12 nonrandomized intervention studies that examined ongoing exercise identified a decrease in progesterone after exercise training (133, 143), with the remaining studies showing no change from baseline. Nonrandomized interventions that examined the acute response of progesterone to a single session of exercise described a brief increase that returned to baseline following recovery (60–62, 67, 79, 81, 83, 94, 96). This was more evident in the luteal phase (81, 83, 94, 96). There was only one relevant observational study, which did not identify an association between weekly physical activity and progesterone levels (146).

Androgens

Meta-analyses of RCTs identified small reductions in testosterone (11 studies, $n = 1,434$; SMD = -0.11 ; 95% CI = $-0.21, -0.01$; $I^2 = 0\%$), free testosterone (5 studies, $n = 1,187$; SMD = -0.12 ; 95% CI = $-0.23, -0.01$; $I^2 = 0\%$), and DHEA (3 studies, $n = 312$; SMD = -0.23 ; 95% CI = $-0.46, -0.01$; $I^2 = 0\%$) levels following exercise. Androstenedione (5 studies, $n = 868$; SMD = -0.10 ; 95% CI = $-0.23, 0.03$; $I^2 = 0\%$) and DHEAS (4 studies, $n = 309$; SMD = -0.28 ; 95% CI = $-0.56, 0.01$; $I^2 = 8\%$) also declined following exercise, although these effects were not statistically significant.

In nonrandomized interventions, there was no change in resting testosterone levels after ongoing exercise in 10 of 12 studies. In response to acute exercise, testosterone levels increased briefly following exercise then returned to baseline following recovery in some (68, 70, 72, 84, 85, 91, 98, 99, 101, 104), but not all studies (65, 90, 93, 96, 100, 108, 109). The increase was evident in response to both aerobic and strength exercise and during both phases of the menstrual cycle. Both DHEA and DHEAS increased in response to exercise before decreasing in 3 of 5 studies (70, 72, 82).

Results from the prospective cohort studies were inconsistent. One study identified lower levels of testosterone and androstenedione in more physically active postmenopausal women (148). This contrasted with studies that did not identify an association between physical activity and testosterone or androstenedione (6, 147). Physical activity was not linearly associated with a decline in either DHEA or DHEAS in one study (6).

Cortisol

Little evidence of a change in cortisol was evident from a meta-analysis of RCTs (5 studies, $n = 328$; SMD = 0.08 ; 95% CI = $-0.19, 0.35$; $I^2 = 26\%$). Following a single session of exercise, some studies documented no change (58, 59, 88, 100), some documented an increase in cortisol during or immediately following exercise (66, 68, 74, 82, 90, 103, 105, 106), and others identified a decrease in cortisol compared with baseline at the conclusion of exercise or following a recovery period (70, 72, 79, 85, 87, 92, 96, 104). The increase in cortisol levels observed in some studies was greater when exercise was performed in the morning rather than the afternoon and was linearly related to exercise intensity (66, 102). The decrease in levels following exercise observed in other studies was more evident in premenopausal than postmenopausal women and was independent of exercise type and intensity (72, 79, 104). No prospective cohort studies that investigated the effect of physical activity on cortisol were identified.

Grade

Results of the GRADE appraisal are presented in **Table 1**. As the conclusions for each physical activity–sex steroid hormone pathway

are based on evidence from several RCTs, the quality of evidence for all physical activity–sex steroid hormone associations was graded as high. The evidence for estradiol, estrogen, androstenedione, DHEAS, and cortisol was graded moderate, owing to publication and imprecision bias.

Discussion

This systematic review and meta-analysis of the effects of physical activity on sex steroid hormones found that physical activity leads to increases in SHBG and decreases in estradiol, free estradiol, progesterone, testosterone, free testosterone, and DHEA. The review also found evidence of possible decreases in estrone, androstenedione, and DHEAS. There was no clear evidence for an effect on estrogen metabolites or cortisol; however, fewer studies examined these outcomes. For all outcomes, the strength of the evidence was graded moderate to high.

This review has several key strengths. It has employed a robust methodology for identifying, synthesizing, and appraising mechanistic evidence to support biological plausibility for the physical activity–sex hormone–breast cancer pathway. In addition, by considering multiple types of studies, including RCTs, nonrandomized interventions, and prospective cohort studies, we have integrated results generated via several different research approaches. This review also has some limitations that must be considered when interpreting the findings. TeMMPo, which was used to prioritize the sex steroid hormones investigated, uses the quantity of evidence for each exposure – mediator and mediator – outcome relationship to score potential mediators. In this sense, it is more suited to identifying what has been most investigated, rather than what may be most important, or novel mediators which warrant attention. To counter this, we supplemented our TeMMPo search with expert input to aid the selection of mediators (2). Our inclusion criteria excluded populations with pre-existing menstrual or metabolic disorders, as well as elite athletes. While we consider this restriction a strength of the study, as it limits several factors that may bias findings such as the effects of athlete diet or menstrual dysfunction in athletes, it does potentially limit the scope of the conclusions regarding exercise volume and intensity. As with all reviews, it is possible that some relevant studies were overlooked by the search strategy employed. However, after performing a separate systematic search for each physical activity–sex hormone pathway, as well as examining reference lists of key papers, we are confident the findings presented are an accurate reflection of current evidence.

These findings are consistent with previous reviews that have outlined reductions in sex hormone levels in response to physical activity, as well as broader changes in menstrual function following more intense activity (150–152). Although these prior reviews have employed broader inclusion criteria, allowing for studies with participants that experienced menstrual dysfunction or had metabolic conditions, or examined combined diet and exercise interventions, the consistency supports a robust finding. While acknowledging the consistency of our findings, we note several methodologic advantages of the current review: inclusion of epidemiologic as well as intervention evidence; tight inclusion criteria for participants and exposure to ensure accurate effect estimates; an up to date search for all sex hormone pathways; and, appraisal of the overall evidence quality using GRADE.

The strength of evidence for an effect of physical activity on sex steroid hormones was stronger in postmenopausal women owing to the number and quality of RCTs that included postmenopausal women. However, the low heterogeneity in the meta-analyses, as well

Table 1. GRADE evidence table.

Outcome	Study type, number of studies (participant <i>n</i>)	Effect estimates (SMD, 95% CI)	Quality of evidence
SHBG	RCT, 8 (1,353)	0.13 (0.02, 0.24)	High
Estradiol	RCT, 12 (1,452)	−0.22 (−0.37, −0.08)	Moderate ^a
Estrone	RCT, 4 (878)	−0.10 (−0.24, 0.03)	High
Free estradiol	RCT, 5 (1,033)	−0.20 (−0.31, −0.09)	High
Estrogen	RCT, 3 (152)	0.62 (−0.11, 1.35)	Moderate ^b
2-OH-E1	RCT, 3 (520)	−0.03 (−0.20, 0.14)	High
16a-OH-E1	RCT, 3 (520)	0.03 (−0.18, 0.20)	High
Progesterone	RCT, 5 (548)	−0.19 (−0.36, −0.02)	High
Testosterone	RCT, 11 (1,434)	−0.11 (−0.21, −0.01)	High
Free testosterone	RCT, 5 (1,187)	−0.12 (−0.23, −0.01)	High
Androstenedione	RCT, 5 (868)	−0.10 (−0.23, 0.03)	Moderate ^a
DHEA	RCT, 3 (309)	−0.23 (−0.46, −0.01)	High
DHEAS	RCT, 4 (242)	−0.28 (−0.56, 0.01)	Moderate ^a
Cortisol	RCT, 5 (328)	0.08 (−0.19, 0.35)	Moderate ^a

^aGraded down due to potential publication bias.

^bGraded down to imprecision bias.

as results from subgroup analysis and from several nonrandomized intervention studies (71, 136, 141), suggest that the responses of sex hormones to physical activity are unlikely to differ between pre- and postmenopausal women.

There was no clear evidence as to what type of physical activity or exercise has the strongest effect of sex steroid hormones. However, the primary conclusions of this review are based on meta-analyses of RCTs that employed aerobic, resistance, or combined exercise interventions with carefully prescribed frequency, intensity, time, and type. There were no RCTs that directly assessed the impact of nonprescribed physical activity, which encompasses a broader range of movement, movement intensities, and settings than more deliberate exercise, on sex hormones (153). Observational studies that measured self-reported physical activity did, like the meta-analyses, document lower levels of free and bioavailable estradiol as well as higher levels of SHBG in more active women (6, 148). However, results for estradiol and testosterone in these studies were inconsistent (6, 146–148). These studies may have been limited by the use of self-reported measures of physical activity, which can attenuate physical activity–health outcome associations (154). As such, RCTs or Mendelian randomization studies are needed to better understand the effects of different types of physical activity on sex steroid hormone levels. The use of continuous monitoring/wearables devices may also potentially transform the evidence base for physical activity as an exposure.

Although there were no clear differences in effect between aerobic and resistance exercise, with evidence of an effect on sex hormones identified for both modalities, the evidence should be considered stronger for aerobic exercise. This is due to the larger number of RCTs that investigated the effect of aerobic exercise, as well as the number of participants in these studies and the duration of the interventions employed. In individual RCTs, neither the organization (e.g., high intensity interval training compared with continuous moderate to vigorous exercise) nor the total quantity (e.g., 150 minutes or 300 minutes per week) of aerobic exercise affected the effect on sex hormones in pre- or postmenopausal women (27, 28, 44, 45, 50). In observational studies, the relationship between physical activity and sex hormones was clearer for aerobic than resistance exercise, although this may reflect the activity patterns of the participants more than

differences between modalities (155). Also, the association between activity and sex hormones varied little by activity intensity (155).

Physical activity may influence the concentration of sex steroid hormones via several pathways. Low levels of physical activity are associated with increased adiposity and an expansion of peripheral adipose tissue (11), which will facilitate increased aromatization of androgens to estrogens (12, 156). The ability of this review to untangle the direct effect of physical activity on sex hormone levels from the indirect effect via changes in body composition is limited. However, in one RCT included in this review, a decrease in sex hormone levels was present only in the exercisers who lost body fat (50). A mediation analysis of another RCT included in this review suggested that the effect of exercise on sex hormones is at least partially mediated by fat loss (45). In addition, an observational study identified statistically significant effects of physical activity on sex hormones when it did not adjust for BMI, but these effects were no longer significant when BMI was included as a covariate (6). These findings suggest that physical activity–sex hormone associations are, at least somewhat, mediated by body composition; future studies that employ causal mediation techniques may be better able to quantify these effects. This suggests that other weight loss strategies, such as energy restricted diets, could be used to achieve similar effects. However, it is important to note that physical activity is the only intervention strategy that reduces fat mass while preserving lean muscle mass (157).

Physical activity may also influence sex steroid hormones via its effect on SHBG, inflammation, and insulin signaling. In our meta-analysis, physical activity preceded an increase in SHBG, which contributes to the bioavailability of androgens and estrogens (158). Physical inactivity has been associated with increased inflammation, which can promote the upregulation of aromatase and increased production of estrogens by stromal cells of the breast (159, 160). In contrast, increasing physical activity may generate the production and release of anti-inflammatory cytokines while also reducing the production of pro-inflammatory cytokines. Physical inactivity may increase in insulin levels, which in turn may decrease hepatic synthesis of SHBG, increasing the bioavailability of estrogens and androgens (5, 161). Increasing physical activity can increase insulin sensitivity and reduce insulin resistance. These effects can be observed after both an acute bout of physical activity as well as with more regular

physical activity (162, 163). Subsequent systematic reviews by our research group will assess the impact of these pathways on breast cancer risk and determine whether physical activity may modulate them (2).

In pre- and postmenopausal women, physical activity and exercise can cause a decrease in levels of select estrogens, progestogens, and androgens, while stimulating a small increase in SHBG. These results support the biological plausibility of the first part of the physical activity–sex hormone–breast cancer pathway.

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