Linking Physical Activity to Breast Cancer Risk via Insulin/Insulin-Like Growth Factor Signaling System, Part 1

Linking Physical Activity to Breast Cancer Risk via Insulin/Insulin-Like Growth Factor Signaling System, Part 1: The Effect of Physical Activity on the Insulin/Insulin-Like Growth Factor Signaling System

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ABSTRACT

Physical activity may reduce the risk of developing breast cancer via its effect on the insulin/insulin-like growth factor (IGF) signaling system. A systematic review searched for randomized controlled trials (RCT), Mendelian randomization and prospective cohort studies that examined the effects of physical activity on insulin/IGF signaling [IGFs, their binding proteins (IGFBP), and markers of insulin resistance] in adult women. Meta-analyses were performed to generate effect estimates. Risk of bias was assessed, and the Grading of Recommendations Assessment, Development, and Evaluation system used to determine the overall quality of the evidence. Fifty-eight RCTs met our inclusion criteria, no observational or Mendelian randomization studies met the criteria for inclusion. Meta-analyses indicated that physical activity interventions (vs. control) reduced fasting insulin, the Homeostatic Model Assessment for Insulin Resistance and fasting glucose. Physical activity increased IGF-1, but there was no clear effect on IGFBP-3 or the ratio of IGF-1:IGFBP-3. Strong evidence was only established for fasting insulin and insulin resistance. Further research is needed to examine the effect of physical activity on C-peptide and HBA1c in women. Reductions in fasting insulin and insulin resistance following exercise suggest some biological plausibility of the first part of the physical activity–insulin/IGF signaling–breast cancer pathway.

See related article by Drummond et al., p. 2116

Introduction

Compared with women with lower levels of physical activity, women with higher levels of physical activity appear less likely to develop breast cancer (1, 2). While the evidence in support of this association is considered strong (1, 2), the causal nature of this relationship is not certain (3). Causal inference can be improved by gaining a greater understanding of the putative mechanistic pathways underlying the physical activity–breast cancer risk relationship (3).

Physical activity may reduce the risk of developing breast cancer via its effect on the insulin/insulin-like growth factor (IGF) signaling system (4). Observational and experimental evidence demonstrates that physical activity improves glycemic control by increasing insulin sensitivity and insulin-dependent glucose uptake (5–8). Impaired glycemic control appears to increase the risk of breast cancer development and has been associated with poorer breast cancer prognosis (9, 10). The effect of physical activity on insulin sensitivity appears to be influenced, in part, by baseline health (7) and hormonal activity (e.g., cycle phase, hormone replacement therapy; refs. 11–13), as well as physical activity type, intensity, and duration (7, 8). Yet the relationships between physical activity and markers of insulin signaling in women have received less scientific attention than in men (14, 15) and examining the effects in women is an important step in understanding the potential physical activity–insulin/IGF signaling–breast cancer pathway.

Physical activity has also been suggested to affect IGF-1, which has been implicated in breast cancer development (16). However, findings for the effect of physical activity on IGF-1 or insulin-like growth factor binding protein-3 (IGFBP-3) have been inconsistent. Some studies suggest physical activity results in a decrease, some an increase (17), and others no change in these parameters (18, 19). Clarifying these relationships in women is a key step in understanding whether changes in insulin signaling mediate a reduced risk of breast cancer in active women.

The World Cancer Research Fund (WCRF) International and University of Bristol developed a causal evidence synthesis framework for conducting systematic reviews of mechanisms of exposure–cancer associations (20, 21). We outlined this framework, and the associated Text Mining for Mechanism Prioritization (TeMMPo, www.temmpo.org.uk; ref. 21), in our protocol paper (3). We also applied the framework to demonstrate that estrogens, androgens, and sex hormone binding globulin partially explain the physical activity–breast cancer relationship (22, 23). For this review, our objective was to

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determine whether, and to what extent, physical activity affects insulin/IGF signaling in women. A subsequent review will examine the evidence for the effect of the insulin/IGF signaling system on risk of breast cancer (24).

Materials and Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (25). It has been registered on PROSPERO (CRD42020146736) and detailed methods were included in our protocol paper (3). In brief, systematic searches of Medline (Ovid), Embase (Ovid), and SPORTDiscus were performed on February 8, 2021 (Supplementary Materials and Methods, Supplementary Table S1). Peer-reviewed, randomized controlled trials (RCT), prospective cohort studies, and Mendelian randomization studies were eligible for inclusion if they examined the effect of physical activity on insulin signaling in post-menarche women. Outcomes identified by TeMMPo (21) and expert review included IGF-1, IGF-2, IGFBP-1, IGFBP-3, insulin, connecting-peptide (C-peptide), fasting glucose, homeostatic model assessment for insulin resistance (HOMA-IR), homeostatic model assessment for insulin sensitivity, hemoglobin A1c (HbA1c), and quantitative insulin-sensitivity check index. Unlike our review for sex-steroid hormones (23), we excluded interventions that were non-randomized or did not contain a comparison group (i.e., single arm pre-post exercise interventions), as these study designs were deemed to have high risk of bias. We also excluded studies that only examined acute insulin/ insulin signaling responses to physical activity, as these studies are less relevant to the habitual physical activity–breast cancer risk relationship. The Cochrane collaboration tool (26), and risk of bias in non-randomized studies of exposures (27) were used to assess risk of bias in RCTs and observational studies, respectively. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the overall quality of evidence as well as the strength of findings generated (28). 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) with 95% confidence interval (CI)] and funnel plots. Sensitivity analyses meta-analyzed studies with low risk of bias only (i.e., RCTs that satisfied 6/7 criteria on the Cochrane collaboration tool). When heterogeneity (I^2) was identified, subgroup analysis examined whether effect estimates varied according to participant menopausal status or type of physical activity (e.g., aerobic vs. resistance exercise; leisure vs. occupational physical activity). Publication bias was determined via visual inspection of the funnel plots. In addition, to graphically represent the relationship between physical activity 'dose' and changes in insulin signaling, we performed a one-stage random-effects dose–response meta-analysis using the 'drmeta' Stata package (29, 30). The duration/quantity of physical activity per week for each intervention arm/observation category was used as the dose and the SMD/effect estimate between arms/ categories was used as the effect estimate. All statistical analyses were performed using Stata version 16 (Stata Corporation, College Station, Texas, USA).

Results

Search results

Search results are presented in **Fig. 1**. Following removal of duplicates in Covidence software (Covidence), 6,536 title and abstract and 467 full texts were screened by two independent researchers using Covidence, with 59 publications meeting the final inclusion criteria. The most common reason for full text exclusion was an ineligible population (e.g., studies that only included males or did not stratify by sex), followed by study design (e.g., cross-sectional studies, non-randomized interventions). All 59 publications included in the review were from parallel group RCTs (52 distinct RCTs; refs. 17–19, 31–86). No prospective observational studies or Mendelian randomization studies met the inclusion criteria.

Study characteristics

Study characteristics are presented in Supplementary Materials and Methods, Supplementary Table S2. Briefly, study populations included premenopausal (RCT = 19), perimenopausal (RCT = 2), and postmenopausal (RCT = 32) women. Study sample size ranged from 16 to 391 women. Intervention type included aerobic (RCT = 26), resistance (RCT = 19), combined aerobic and resistance (RCT = 10), or other exercise (RCT = 3, including Yoga, aqua therapy, and Taekwondo). The median intervention duration was 14 weeks, and these ranged from 8 weeks to 12 months. Comparisons included an inactive or usual activity control (RCT = 41), different type of physical activity program (RCT = 12), or a different 'dose' of physical activity (RCT = 9). Outcomes included: levels of circulating glucose (RCT = 30); insulin (RCT = 30); insulin resistance (RCT = 24); insulin sensitivity (RCT = 4); IGF-1 (RCT = 24); IGF-2 (RCT = 2); IGFBP-1 (RCT = 3); IGFBP-3 (RCT = 7); IGF-1:IGFBP-3 (RCT = 5); C-peptides (RCT = 1); and HBA1c (RCT = 1).

Risk of bias

Risk of bias results are presented in Supplementary Materials and Methods, Supplementary Table S3. All studies scored high for performance bias as it was not possible to blind participants from the exercise they were completing. Five studies were judged to have low bias for all other categories (18, 19, 43, 52, 69). The remaining studies were judged to have high bias for participant attrition (18 RCTs; refs. 32, 34–37, 39, 49, 53, 59, 60, 62, 73, 75, 81–85), unclear selection bias e.g., insufficient information on randomization (40 RCTs; refs. 17, 31, 32, 34–36, 38–42, 44–49, 53–57, 61, 63–66, 71–76, 78–80, 83–86), and unclear other bias e.g., no information on assay sensitivity provided (15 RCTs; refs. 31, 33, 36, 38, 39, 41, 44–46, 62, 81, 82, 85, 86).

Effects of physical activity on the insulin/IGF signaling system

Meta-analysis forest plots for studies comparing a physical activity intervention to a usual activity control are presented in **Fig. 2** (fasting glucose, fasting insulin, and HOMA-IR) and **Fig. 3** (IGF-1, IGFBP-3, and IGF-1:IGBP-3). Results of sensitivity analysis and subgroup analysis are presented in Supplementary Materials and Methods, Figs. S1–S6. Funnel plots are presented in Supplementary Materials and Methods, Supplementary Fig. S7. The dose–response meta-analysis graphs are presented in **Fig. 4**. These graphs contained studies that compared physical activity with a usual activity control and comparisons of different physical activity interventions. Results of individual studies that were not included in meta-analyses are presented in Supplementary Materials and Methods, Supplementary Table S4.

Glucose

Meta-analysis of RCTs identified a small decrease in fasting glucose following exercise interventions compared with a usual activity control (studies = 20, n = 1,454, SMD = –0.17, 95% CI = –0.34 to –0.01, I^2 = 49%). However, as there was moderate heterogeneity in this effect

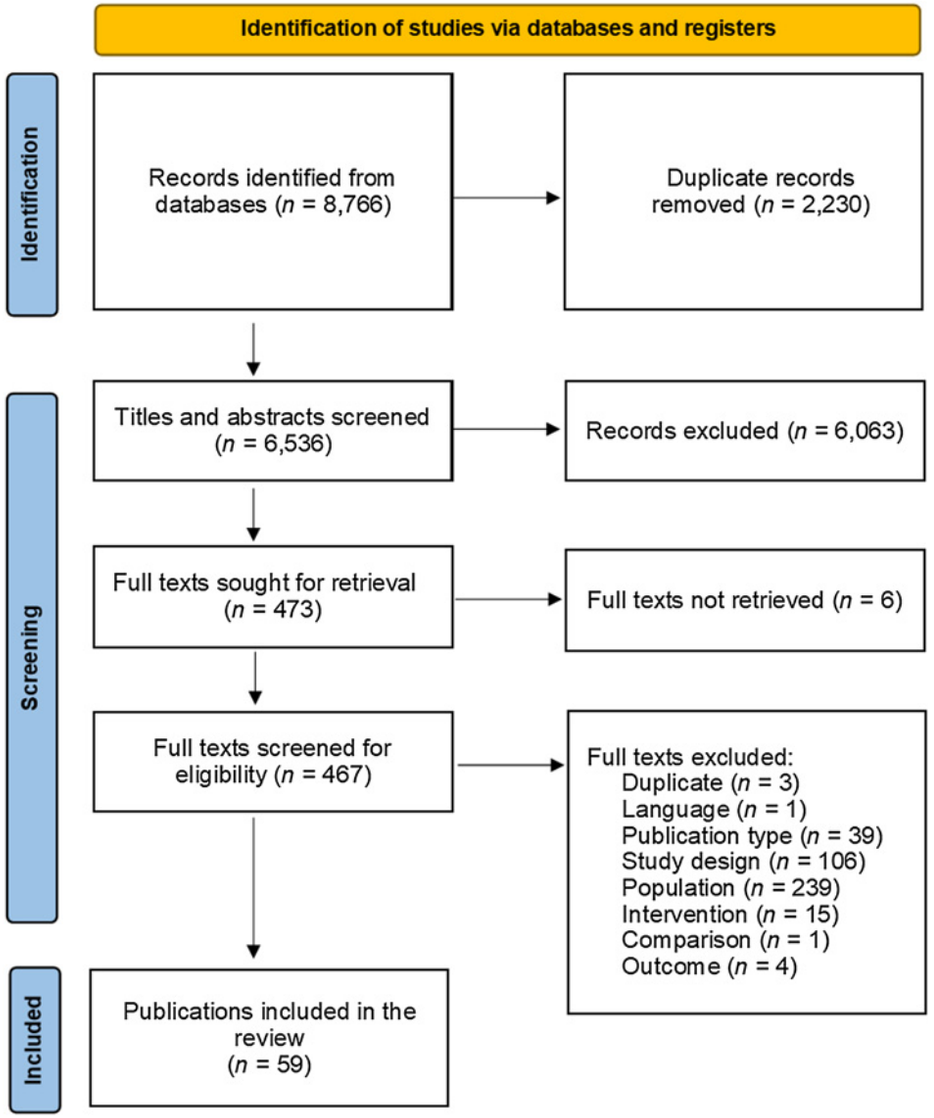


Figure 1.
PRISMA flow diagram. This figure incorporates literature search, screening and study selection.

estimate and the sensitivity analysis restricted to studies with low risk of bias only reported an effect half the size (studies = 3, n = 663, SMD = –0.08, 95% CI = –0.25 to 0.09, I^2 = 17%), there is limited certainty in this finding. There was no clear dose–response effect of physical activity minutes per week on fasting glucose (**Fig. 4A**).

Subgroup analysis identified a decrease in fasting glucose in women who were postmenopausal (studies = 11, n = 882, SMD = –0.24, 95% CI = –0.46 to –0.03, I^2 = 47%) but not in women who were premenopausal (studies = 8, n = 545, SMD = –0.04, 95% CI = –0.32 to 0.23, I^2 = 42%). There was some evidence of decrease for aerobic physical activity (studies = 13, n = 1,225, SMD = –0.11, 95% CI = –0.30 to 0.08, I^2 = 51%), but little evidence of an effect for resistance training alone (studies = 3, n = 111, SMD = 0.03, 95% CI = –0.34 to 0.39, I^2 = 0%). Decreases in fasting glucose were evident following combined aerobic and resistance training (studies = 5, n = 125, SMD = –0.54, 95% CI = –0.89 to –0.19, I^2 = 0%). The other type of physical activity included in the meta-analysis was Yoga (studies = 1, n = 16, SMD = –1.05, 95% CI = –2.05 to –0.05, I^2 = NA). The robustness of these subgroup findings was limited by moderate heterogeneity.

In individual studies not included in the meta-analysis, there was little evidence of differences in glucose levels based on the quantity of aerobic exercise in a 12-month intervention (52), and a suggestion that resistance training had a greater effect on glucose concentrations than aerobic training (46).

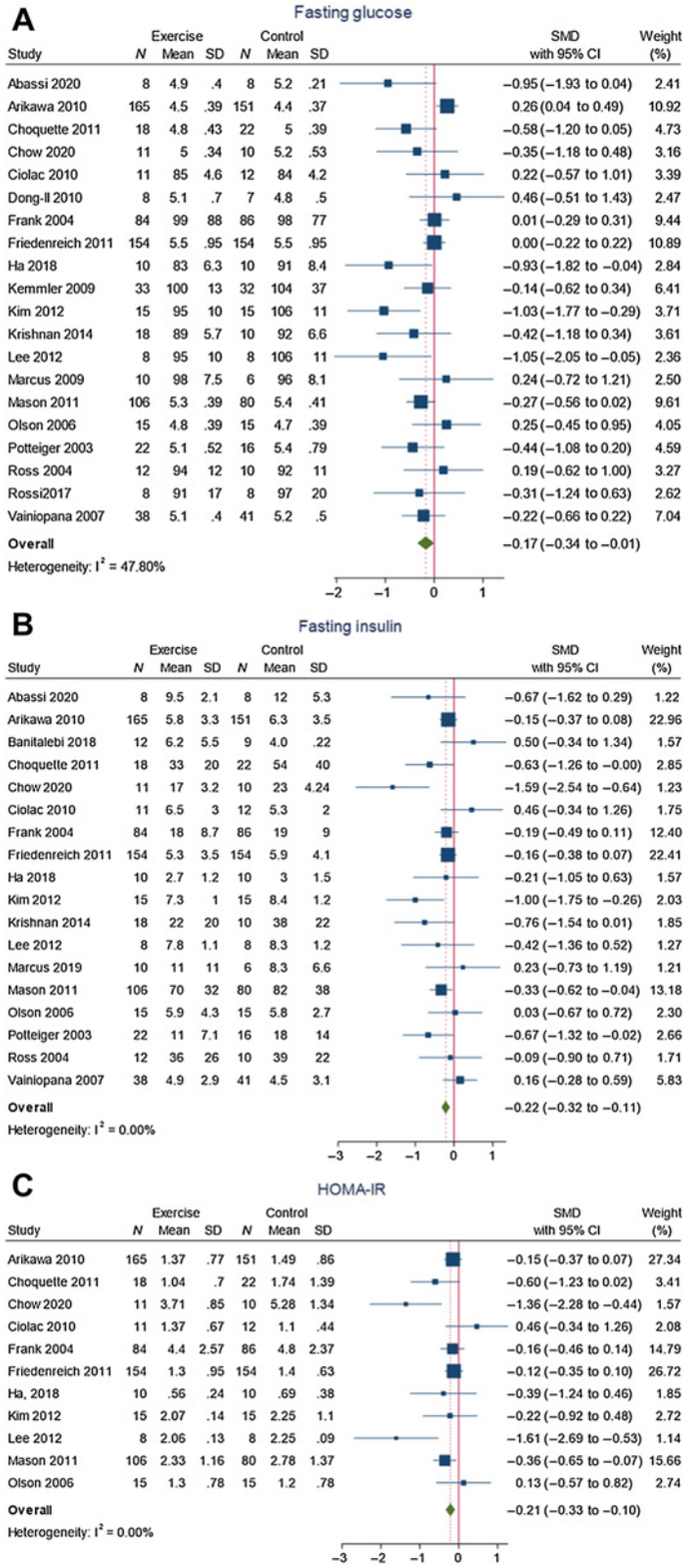
Insulin

Meta-analysis suggested a decrease in fasting insulin following exercise compared with usual activity controls (studies = 18, n = 1,380, SMD = –0.22, 95% CI = –0.32 to –0.11, I^2 = 0%). Sensitivity analysis did not change the results (Supplementary Materials and Methods, **Fig. 2**). The meta-analysis included aerobic, resistance, combined exercise, and yoga interventions, and, as there was no heterogeneity, no subgroup analysis was performed. The dose–response meta-analysis identified that fasting insulin decreased with intervention duration, with decreases most evident from 150 minutes per week (**Fig. 4B**).

Individual RCTs that were not included in the meta-analysis did not suggest differences in fasting insulin according to exercise bout

Figure 2.

Forest plots for effects of physical activity interventions compared with usual activity control. Forest plot for (**A**) fasting glucose, (**B**) fasting insulin, and (**C**) HOMA-IR.



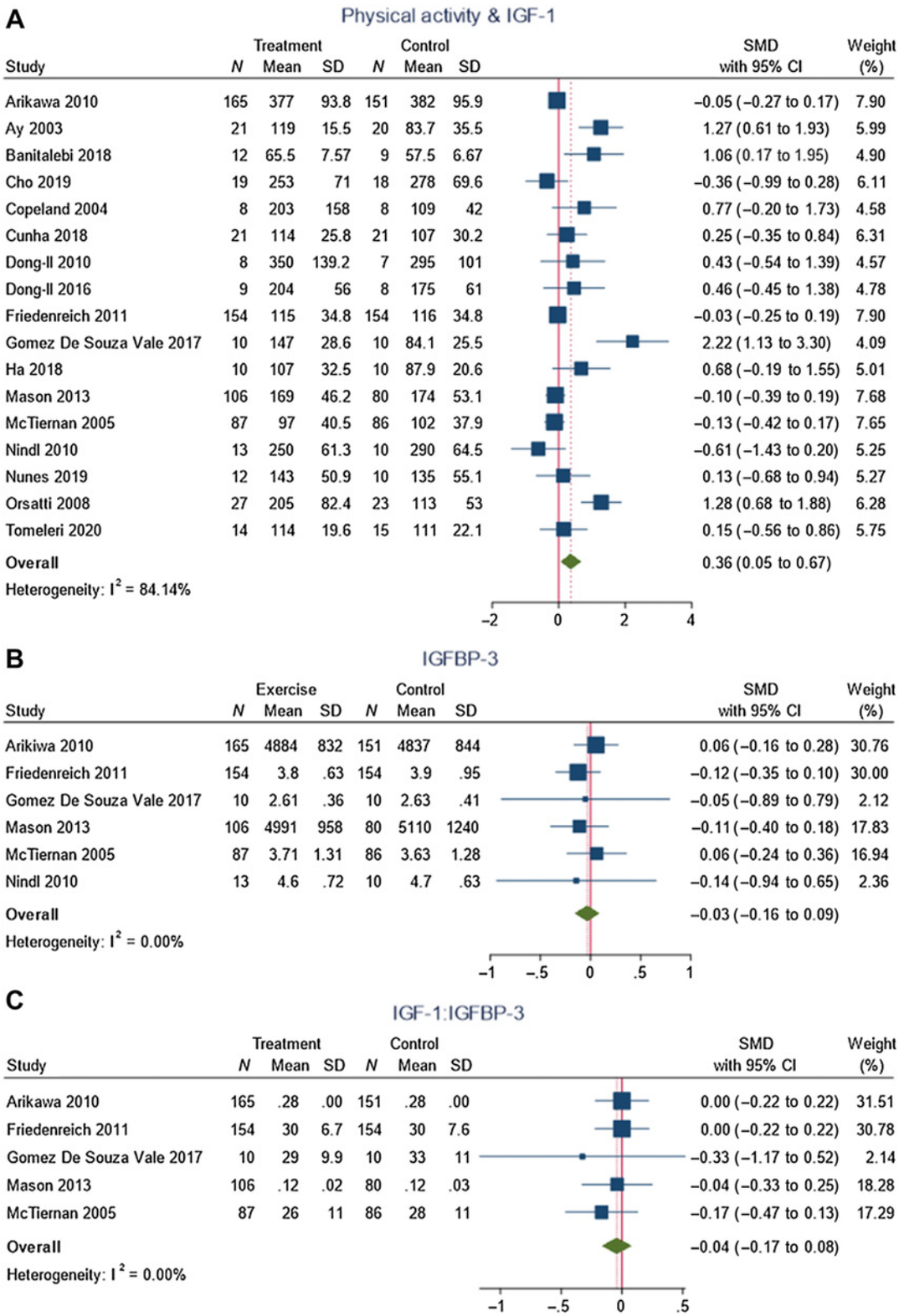


Figure 3.
Forest plots for effects of physical activity interventions compared with usual activity. Forest plot for (**A**) IGF-1, (**B**) IGFBP-3, and (**C**) IGF-1:IGFBP-3.

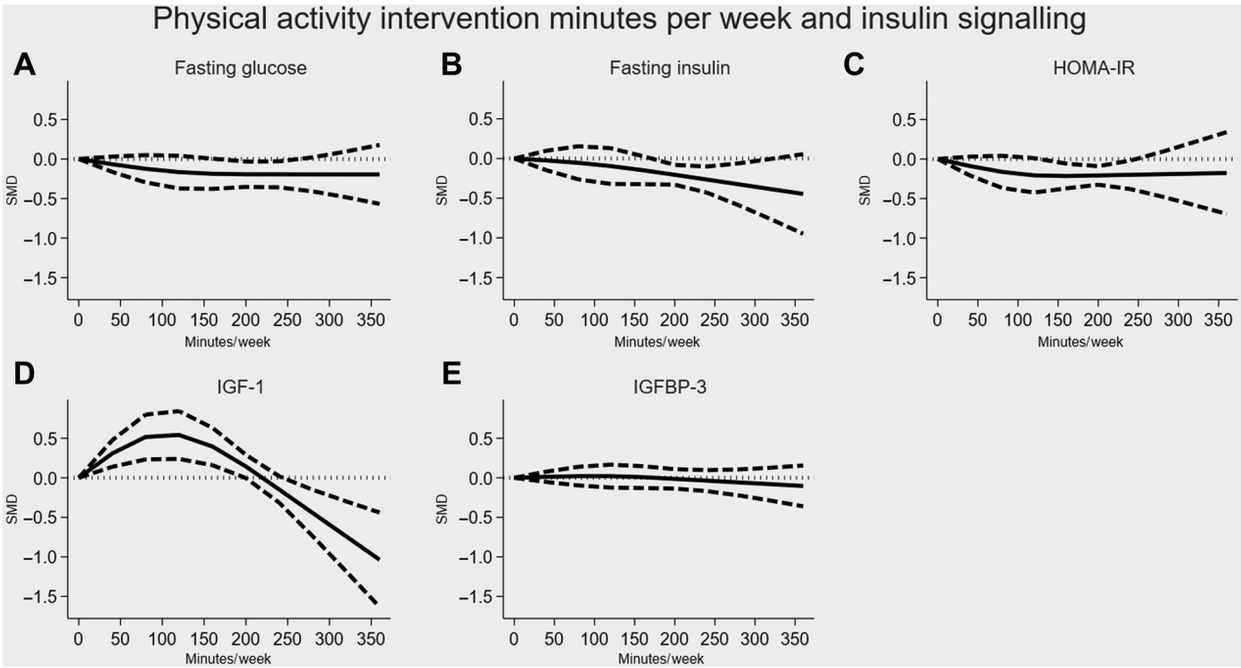


Figure 4.

Dose–response meta-analysis for physical activity intervention minutes per week. Dose–response plot for (**A**) fasting glucose, (**B**) fasting insulin, (**C**) HOMA-IR, (**D**) IGF-1, (**E**) IGFBP-3, and (**F**) IGF-1:IGFBP-3. The dose for inactive or usual activity control groups was set to 0 minutes per week.

duration (52), weekly quantity (64), or structure (i.e., continuous vs. interval walking; ref. 44). High intensity interval training (HIIT) was more likely to decrease insulin levels than continuous moderate intensity aerobic exercise (83). Resistance training produced greater decreases in insulin than HIIT (33).

C-Peptide

One study examined the relationship between exercise and C-peptide. C-peptide concentrations decreased from baseline after 12 months of aerobic exercise in postmenopausal women; however, this decrease was not evident when compared with usual activity controls (67).

HOMA-IR

Meta-analysis identified a decrease in HOMA-IR following aerobic, resistance, or combined exercise compared with a usual activity control (studies = 11, n = 1,160, SMD = –0.21, 95% CI = –0.33 to –0.10, I^2 = 0%). This finding did not change following sensitivity analysis. The dose–response meta-analysis analysis showed a slight decrease at lower durations of physical activity which plateaued from around 100 minutes per week (**Fig. 4C**).

In individual RCTs that were not included in the meta-analysis, there was evidence that walking (44), continuous aerobic exercise (52), HIIT (33, 83), and resistance training decreased HOMA-IR (33, 79). These decreases were still evident 12 months after no intervention (52). There was no evidence for a different effect of aerobic exercise structure or quantity (44, 52), but the effect may have been greater for resistance training (33).

HBA1c

One RCT examined change in HBA1c% following aerobic exercise performed by premenopausal women. HBA1c% decreased with time but there was no clear effect for exercise intensity or setting (i.e., supervised hospital vs. home based; ref. 37).

IGF-1

Meta-analysis suggested that physical activity results in a small increase in IGF-1 levels (studies = 17, n = 1,316, SMD = 0.36, 95% CI = 0.05 to 0.67, I^2 = 84%). However, this result had high heterogeneity and likely publication bias as per the funnel plot (Supplementary Materials and Methods, Supplementary Fig. S7). There was no clear effect of physical activity following sensitivity analysis (studies = 4, n = 709, SMD = –0.07, 95% CI = 0.23 to 0.08, I^2 = 0%). The dose–response analysis illustrated an inverted-U shape, indicating an increase in IGF-1 levels as a result of shorter duration interventions compared with 0 minutes/week, but a decrease in IGF-1 resulting from longer duration interventions (**Fig. 4D**).

Subgroup analysis identified differences between types of physical activity. There was little evidence of an effect of aerobic (studies = 7, n = 1,042, SMD = –0.05, 95% CI = –0.17 to 0.07, I^2 = 0%) but evidence of a difference following resistance exercise (studies = 9, n = 244, SMD = 0.61, 95% CI = 0.20 to 1.03, I^2 = 0%). A positive effect was identified in postmenopausal (studies = 14, n = 976, SMD = 0.42, 95% CI = 0.08 to 0.76, I^2 = 82%) but not premenopausal women (studies = 3, n = 360, SMD = 0.10, 95% CI = –0.76 to 0.95, I^2 = 82%); however, these were again limited by high heterogeneity. The other types of physical activity included in the meta-analysis were aquatic based exercise (studies = 2, n = 61, SMD = 0.84, 95% CI = –0.09 to 1.76, I^2 = 67%) and Taekwondo (studies = 1, n = 37, SMD = –0.36, 95% CI = –0.99 to 0.28, I^2 = NA).

One individual RCT did not show change in IGF-1 levels following aerobic exercise (49). Three studies did not show change following resistance exercise (71–73). One study showed an increase in total

IGF-1 following resistance training and combined training but not aerobic training (55).

IGFBPs

Meta-analysis did not show a change in IGFBP-3 levels following physical activity (studies = 6, n = 1,026, SMD = 0.03, 95% CI = –0.16 to 0.09, I^2 = 0%). These results were consistent across all sensitivity and dose–response analyses (**Fig. 4E**).

Two RCTs showed no change or an increase in IGFBP-3 levels following physical activity interventions (55, 71). For IGFBP-1, two RCTs found no effect of physical activity (35, 74). One study identified a decrease from baseline values after training (55).

IGF-1:IGFBP-3

Meta-analysis did not show a change in the IGF-1:IGFBP-3 ratio following exercise (studies = 5, n = 1,003, SMD = –0.04, 95% CI = –0.17 to 0.08, I^2 = 0%). These results did not change following sensitivity analysis that only examined studies with lower risk of bias.

Grade

Results of the GRADE appraisal are presented in **Table 1**. The quality of evidence for each physical activity–insulin signaling outcome that was meta-analyzed was initially graded as high, based on the many parallel group RCTs available. The evidence relating to fasting glucose was downgraded to low due to the level of heterogeneity, imprecision in the finding, and reduction in effect size when studies were limited to low risk of bias. The evidence relating to IGF-1 was downgraded to low because of high heterogeneity and clear publication bias. None of these outcomes met the criteria to be upgraded. For outcomes that were not meta-analyzed (i.e., C-peptide, HBA1c, and IGFBP-1), a GRADE judgement of very low was given owing to the limited evidence identified.

Discussion

There was strong evidence that physical activity interventions decrease fasting insulin and insulin resistance and low-quality evidence that physical activity decreases fasting glucose in women. There was also low-quality evidence that physical activity increases IGF-1; however, this relationship was complex and potentially influenced by activity type and quantity. There was little evidence of an effect of physical activity on IGFBP-3 or the IGF-1: IGFBP-3 ratio.

Table 1. GRADE appraisal for physical activity–insulin/IGF signaling pathways.

Outcome	Meta-analysis study n (participant n)	Meta-analysis effect estimate SMD (95% CI)	GRADE judgment
Fasting glucose	20 (1,454)	–0.17 –0.34 to –0.01)	Low[a]
Fasting insulin	18 (1,380)	–0.22–0.32 to –0.11)	High
HOMA-IR	11 (1,160)	–0.21–0.33 to –0.10)	High
C-Peptide	NA	NA	Very low[b]
HBA1c	NA	NA	Very low[b]
IGF-1	76 (1,316)	0.36 (0.05–0.67)	Low[c]
IGFBP-1	NA	NA	Very low[b]
IGFBP-3	6 (1,026)	0.03 (–0.16, 0.09)	High
IGF-1: IGFBP-3	5 (1,003)	–0.04 (–0.17, 0.08)	High

[a]Graded down due to heterogeneity, imprecision, and change in effect size following sensitivity analysis.
[b]Graded down due limited study numbers.
[c]Graded down due to heterogeneity and publication bias.

While the findings of this systematic review and meta-analysis draw on a several high quality RCTs, there are limitations that must be considered when interpreting the findings. As the overarching aim of this review is to determine whether insulin signaling may mediate the physical activity–breast cancer relationship, we excluded studies that did not present results for women separate from men. This in turn limited the number and type of studies that met the inclusion criteria. The inclusion criteria were also limited to women who were free from medical conditions and not using medications that may influence metabolic outcomes. Although this is a strength, as it reduces potential sources of bias, previous research has indicated that individuals with poorer metabolic health may experience greater metabolic benefit from exercise (7, 8). As such, excluding these participants may have limited the size of exercise–insulin/IGF signaling effect estimates. The dose–response meta-analysis examining minutes per week of physical activity interventions and insulin/IGF signaling represents a novel contribution to the literature; however, this remains somewhat crude as it is not able to capture complexities such as exercise type, structure, or intensity. There were also limitations of the literature to note. For example, most interventions featured supervised and highly structured aerobic, resistance, or combined exercise programs. While this allows more certainty about the influence of specific exercise program components on insulin signaling, these interventions do not always reflect the type of physical activity people complete in real world settings, e.g., walking or cycling for transport, or gardening at home. Unfortunately, no observational studies could be included in our review, which could provide more evidence on associations of real-life physical activity levels with insulin signaling. Further, 18 of the 59 RCTs had >10% attrition or intervention noncompliance. This makes it more difficult to discern the 'true' effect of exercise; however, it may also reflect normal behavior for exercise participation.

A decrease in fasting glucose, fasting insulin, and insulin resistance is consistent with previous reviews and clinical guidelines (7, 8, 87). For example, a 2017 meta-analysis of seven RCTs identified reduced insulin and insulin resistance following structured exercise in postmenopausal women (87). In the current review, the absence of heterogeneity in the fasting insulin or insulin resistance meta-analyses suggest that all types of physical activity studied (i.e., aerobic, resistance, and combined exercise) may offer benefit for these outcomes; however, for fasting glucose, sub-group analysis suggested combined aerobic and resistance exercise resulted in the largest decrease. Collectively, these findings are consistent with content provided in clinical guidelines that outline improvements in insulin/IGF signaling following any type of exercise but suggest combined aerobic and resistance training may offer the greatest benefit (7). Our dose–response meta-analysis did not identify a clear dose–response relationship between physical activity intervention minutes per week and glucose, insulin, or insulin resistance. This was somewhat unexpected, with a prior review noting that greater exercise volumes have been associated with greater increases in insulin sensitivity (8). However, this finding has not been unanimous, is more evident in populations with pre-existing metabolic conditions (8), and much of the previous literature has focused on men (14, 15).

Exercise type and quantity also appeared to influence IGF-1 concentrations. In sub-group analysis, while aerobic exercise appeared to have minimal discernible effect, performing resistance exercise

preceded an increase in IGF-1 concentrations. The increase in IGF-1 following resistance exercise may reflect muscle adaption that occurs following resistance but not aerobic exercise, with prior research documenting increases in IGF-1 with increases in muscle strength (88). In the dose–response analysis, increases in IGF-1 were evident in interventions that had lower weekly intervention minutes but decreased with higher minute/ week interventions. This curvilinear shape is like that described for body mass index (BMI) and IGF-1, where both a lower and higher BMI have been associated with lower circulating levels of IGF-1 compared with a normal range BMI (89). One potential explanation may be the utility of circulating IGF-1 as an indicator of metabolic stress (88). Or that exercises optimizes systemic IGF concentrations (90). However, overall, the strength of evidence for a physical activity–IGF-1 relationship was graded as low, making definitive conclusions difficult. Mechanistic reviews of exercise and IGF-1 note the complexity of IGF-1 regulation and differing exercise responses of local and circulating IGF-1 as challenges to current understanding (88).

As with our recent review examining physical activity and sex hormones (23), the strength of the evidence was stronger in postmenopausal compared with premenopausal women owing to the larger number of high-quality RCTs that featured postmenopausal women only. However, as there was no heterogeneity for insulin and insulin resistance outcomes, and as sub-group analysis by menopause status for fasting glucose and IGF-1 did not appear to reduce heterogeneity for these outcomes, the effects of physical activity on the insulin/IGF signaling system do not appear to differ greatly by menopause status.

Several recommendations can be made to improve the quality and scope for the evidence for physical activity to the insulin/IGF signaling system in women. To reduce the risk of bias in RCTs with lower exercise compliance, we recommend using methods that can mitigate the effect of attrition, such as inverse probability weighting or generalized methods (91, 92). Beyond this, there is a need to determine the effectiveness of increasing unstructured physical activity on metabolic outcomes as the meta-analyses only included one Yoga intervention and one Taekwondo intervention. It did not contain other alternative physical activity interventions. Emulating target trials using cohort study data that includes real-life types of physical activity and sedentary behavior is one approach that may be used to estimate the causal effects of physical activity (93).

The overarching aim of this series of reviews is to clarify which pathways may underlie the reduction in breast cancer risk that is associated with higher levels of physical activity. While the decreases identified for fasting glucose, fasting insulin, and insulin resistance support the biological plausibility of the first part of a physical activity–insulin/IGF signaling system–breast cancer pathway, the findings for IGF-1 and IGFBP-3 do not. Part 2 of this review examines the evidence for these insulin signaling biomarkers and breast cancer risk (24).

Authors' Disclosures

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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