Linking Physical Activity to Breast Cancer: Text Mining Results and a Protocol for Systematically Reviewing Three Potential Mechanistic Pathways

Brigid M. Lynch[1,2,3], Roger L. Milne[1,2,4], Dallas R. English[1,2], Kristy A. Brown[5], Ann E. Drummond[1], Christopher T.V. Swain[1], Eline H. van Roekel[6], Melissa M. Moore[7], Tom R. Gaunt[8], Richard M. Martin[8,9], and Sarah J. Lewis[8]

ABSTRACT

Epidemiologic research suggests that physical activity is associated with a reduced risk of breast cancer, but the causal nature of this link is not clear. Investigating mechanistic pathways can provide evidence of biological plausibility and improve causal inference. This project will examine three putative pathways (sex steroid hormones, insulin signaling, and inflammation) in a series of two-stage systematic reviews. Stage 1 used Text Mining for Mechanism Prioritisation (TeMMPo) to identify and prioritize relevant biological intermediates. Stage 2 will systematically review the findings from studies of (i) physical activity and intermediates and (ii) intermediates and breast cancer. Ovid MEDLINE, EMBASE, and SPORTDiscus will be searched using a combination of subject headings and free-text terms. Human intervention and prospective, observational studies will be eligible for inclusion. Meta-analysis will be performed where possible. Risk of bias will be assessed using the Cochrane Collaboration tool, or the ROBINS-I or ROBINS-E tool, depending on study type. Strength of evidence will be assessed using the GRADE system. In addition to synthesizing the mechanistic evidence that links physical activity with breast cancer risk, this project may also identify priority areas for future research and help inform the design and implementation of physical activity interventions.

See related reviews by Swain et al., p. 16 and Drummond et al., p. 28

Introduction

Breast cancer accounts for around one quarter of all female cancers and is the leading cause of cancer-related death among women globally (1). Epidemiologic research suggests physical activity may protect against the development of breast cancer. Engaging in moderate physical activity is associated with a reduction in the risk of postmenopausal breast cancer of approximately 13%, while vigorous physical activity has been associated with risk reductions of 9 and 17% for pre- and postmenopausal breast cancer, respectively (2). Although the evidence in support of these associations has been described as strong, the observational design, typically with one exposure assessment, of studies included in the Continuous Update Project Report make it difficult to draw firm conclusions regarding causality (2).

Several mechanistic pathways underpinning the association between physical activity and breast cancer have been proposed (3). Increased exposure to sex steroid hormones increases breast cancer risk (4–7). The expression of estrogen and progesterone receptors in a tumor are positive prognostic indicators, and breast cancer treatments that target these pathways remain the most effective (4). Furthermore, androgens can stimulate the growth of breast cancers, either by a direct action or following aromatization to estrogen (8). Physical activity may therefore reduce breast cancer risk via its effect on female sex hormones (3). In premenopausal women, there is some evidence to suggest that vigorous physical activity can disrupt regular menstrual function (9), and, when combined with energy restriction, may result in delayed onset of menarche (10, 11). Intervention studies suggest that vigorous physical activity results in small reductions in total and free estrogen and estradiol levels in healthy premenopausal women, changes that are not completely explained by anthropometric change (9, 12). Among postmenopausal women, numerous randomized controlled trials (RCT) have demonstrated that moderate or vigorous aerobic physical activity reduces both total estradiol and free estradiol, and increases sex hormone–binding globulin (SHBG; ref. 12).

It has also been proposed that insulin resistance increases breast cancer risk (13–15). Insulin resistance necessitates an increase in production of insulin by pancreatic beta cells to maintain normal glucose levels (15). Insulin can enhance tumor development directly through stimulating cellular proliferation and via activation of the insulin like growth factor (IGF-I) system, which mediates cellular differentiation, proliferation, and apoptosis (15–17). Insulin can also regulate the synthesis and availability of sex hormones (18). Increased

[1]Cancer Epidemiology Division, Cancer Council Victoria, Victoria, Australia. [2]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. [3]Physical Activity Laboratory, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia. [4]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Melbourne, Victoria, Australia. [5]Department of Medicine, Weill Cornell Medicine, New York, New York. [6]Department of Epidemiology, GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands. [7]Medical Oncology, St Vincent's Hospital, Melbourne, Victoria, Australia. [8]Bristol Medical School, University of Bristol, Bristol, United Kingdom. [9]NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, United Kingdom.

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

Systematic review registration: These reviews have been prospectively registered on PROSPERO: 2020 CRD42020146736; CRD42020165696; CRD42020165689.

Corresponding Author: Brigid M. Lynch, Cancer Epidemiology Division, Cancer Council Victoria, 615 St Kilda Road, Melbourne, Victoria 3004, Australia. Phone: 613-9514-6209; E-mail: brigid.lynch@cancervic.org.au

Cancer Epidemiol Biomarkers Prev 2022;31:11–5

doi: 10.1158/1055-9965.EPI-21-0435

insulin sensitivity is an adaptive response to physical activity (19). An acute bout of physical activity precedes an increase in insulin-stimulated glucose uptake in the exercised skeletal muscle that lasts for up to 48 hours (19, 20). Regular physical activity leads to improvements in whole body as well as skeletal muscle insulin sensitivity via increases in GLUT4 receptor number and function, muscle capillarization, and blood flow (19, 21, 22). Physical activity has also been associated with lower levels of IGF-I and increased levels of insulin-like growth factor-binding protein 3, which binds to IGF-I, reducing its bioavailability (23).

Inflammation has been implicated in the etiology of most cancers (3, 24). Inflammation stimulates cell proliferation, tumor microenvironmental changes and oxidative stress, which can deregulate normal cell growth and promote malignant conversion and progression (25). Adipose tissue secretes multiple biologically active polypeptides, many of which are proinflammatory cytokines (referred to as adipokines; refs. 26, 27). Adipokines may play a role in the development of insulin resistance, as leptin and adiponectin enhance insulin sensitivity through activation of adenosine monophosphate protein kinase (26). Adipokines might also increase breast cancer risk by affecting estrogen biosynthesis and activity (28). Observational research supports an association between lower levels of physical activity and an adverse, chronic inflammatory profile (29, 30). Physical activity interventions demonstrate that regular activity induces expression of anti-inflammatory cytokines and suppresses the expression of pro-inflammatory cytokines in the general population, as well as elderly and obese populations (31, 32).

This brief summary of these putative mechanisms is based on narrative reviews that are common in the literature, and a small number of human trials and experimental studies. Narrative reviews may be biased, and lead to erroneous conclusions being drawn (33). Thus, there is a strong need for more rigorous reviews of the total body of mechanistic evidence. Systematic review, synthesis of data subject to quality appraisal, and where possible, meta-analysis, will provide greater insight into the plausibility and strength of evidence that supports these pathways. The World Cancer Research Fund (WCRF) International and the University of Bristol have developed a novel framework for generating an overview of biological pathways and undertaking systematic reviews of mechanistic research relating to exposure–outcome associations (33). The framework, which has been independently validated (34), provides a protocol for synthesizing mechanistic research.

Our aim is to use the WCRF International/University of Bristol framework to synthesize key putative mechanistic pathways underlying the association of physical activity with reduced breast cancer risk. We will take a targeted approach, focusing on the molecular pathways most frequently discussed in the literature, namely: (i) sex steroid hormones; (ii) insulin signaling; and (iii) inflammation (pro- and anti-inflammatory markers).

Methods

Our series of systematic reviews to examine three intermediate pathways (sex steroid hormones, insulin signaling, and inflammation) that may connect physical activity and breast cancer risk will each contain two stages. While it is understood that there is interplay between these three pathways, for the purpose of the systematic reviews we treat these as separate etiological functions.

Stage 1 (completed; results are presented below) used an automated process, "Text Mining for Mechanism Prioritisation" (TeMMPo; ref. 35), to quantify and visualize the amount of evidence for specific intermediate phenotypes within the three intermediate pathways. As the quantity of evidence available may not reflect more recent and less researched developments in the scientific literature, TeMMPo results were combined with expert input to ensure all key pathways were identified.

Stage 2 comprises systematic reviews of intermediate phenotypes identified in stage 1. The protocol for stage 2 is structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (36), and is presented in this article. The reviews have been registered with PROSPERO (International prospective register of systematic reviews: CRD42020146736; CRD42020165696; CRD42020165689).

Stage 1 - prioritization of intermediates

Medical subject headings (MeSH) for exposure, intermediate and outcome, relevant to each pathway were entered into TeMMPo (Supplementary Table S1) and used to generate a comprehensive list of intermediate phenotypes for each pathway and produce a graphical representation (Sankey plot; ref. 33) of intermediate phenotypes potentially mediating the physical activity–breast cancer association. The top scoring intermediates for each pathway were reviewed by study investigators for relevance and biological plausibility, according to a predefined inclusion and exclusion criteria (Supplementary Tables S2–S4). Expert input was also sourced to identify potentially relevant intermediates not identified by TeMMPo. Intermediates were identified via the text mining process and those added based on expert review are clearly demarcated in the results. The prioritized intermediates were then grouped into categories based on type (e.g., estrogens or androgens), before moving on to systematic review.

Table 1 presents the final list of steroid sex hormones selected for systematic review; after review of the intermediates prioritized by

Table 1. Intermediates for sex steroid hormones included in systematic reviews.

Steroid type	Prioritized intermediate
Estrogen	Estradiol
	Hydroxyestrones
	Estrogens, catechol
	Estradiol congeners
	Estrone
	Estriol
Progesterone	Progesterone
	Pregnanediol
	Progesterone congeners
	17-alpha-Hydroxyprogesterone
	Pregnenolone
Androgens	Testosterone
	Dehydroepiandrosterone
	Androstenedione
	Dihydrotestosterone
	Testosterone congeners
	Androstenediol
	Etiocholanolone
	Androsterone
	Androstane-3,17-diol
	Epitestosterone
Glucocorticoids	Cortisol[a]
Other	Sex hormone–binding globulin

[a]Intermediates added based on expert review.

Table 2. Intermediates for insulin signaling included for systematic review.

	Prioritized intermediate
IGFs	Insulin-like growth factor I
	Insulin-like growth factor II
	Insulin-like growth factor binding protein 1
	Insulin-like growth factor binding protein 3
Insulin resistance	Insulin
	Pro-insulin
	C-peptide
	Fasting glucose
	HOMA-IR[a]
	HOMA-S[a]
	HbA1c[a]
	QUICKI[a]

[a]Intermediates added based on expert review.

TeMMPo, the investigator team decided that glucocorticoids should be added to the list. Although not a sex hormone, glucocorticoids belong to the same steroid superfamily as estrogen, androgens, and progestogens. **Table 2** presents the final list of insulin signaling biomarkers for inclusion in the systematic reviews (HOMA-IR, HOMA-S, HbA1c, and QUICKI were added based on expert input), and **Table 3** presents the final list of inflammatory biomarkers for systematic review (the investigator team decided that interferon-gamma and chemokine ligand 2 should be added to the intermediates prioritized by TeMMPo).

Stage 2 – systematic review of mechanistic pathways

Using the WCRF International/University of Bristol framework, we will systematically review the published research relating to (i) physical activity and prioritized intermediates, and (ii) prioritized intermediates and breast cancer risk. These systematic reviews will help to clarify the causal pathways by which physical activity helps prevent breast cancer.

Inclusion and exclusion criteria

Intervention trials, Mendelian randomization studies, and prospective cohort studies will be eligible for inclusion. Neither cross-sectional nor case–control studies will be eligible due to the likely serious bias arising from timing of exposure and outcome collection. Participants will include human postpubescent (i.e., has experienced menarche) and pre- and postmenopausal women with no prior history of cancer. Studies of women with conditions that may confound exposure–outcome associations (e.g., type II diabetes, polycystic ovarian syndrome) will be excluded. Studies of elite athletes will also be excluded due to the inability to account for the likely effect of diet, as well as the relatively high prevalence of menstrual dysfunction. For the physical activity–intermediate component, the exposure must be physical activity or exercise only (e.g., not an intervention combining exercise and caloric restriction). For the intermediate–breast cancer component, the outcome must be cancer incidence. Studies examining carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS) will be excluded as they are both precancerous and noninvasive. Only studies in English will be eligible for inclusion.

Table 3. Intermediates for inflammation included for systematic review.

	Prioritized intermediate
Cytokines	Tumor-necrosis factor-α
	Interleukin-1
	Interleukin-6
	Interleukin-8
	Interleukin-10
	Interleukin-13
	Interleukin 1-β
	Interferon-γ[a]
	Chemokine ligand 2[a]
Adipokines	Adiponectin
	Leptin
Other	C-reactive protein

[a]Intermediates added based on expert review.

Search strategy

Relevant publications will be identified through a systematic search of the following electronic databases: PubMed/Ovid MEDLINE (1946–present), Ovid EMBASE (1980–present), and SPORTDiscus (1930–present). Two sets of searches will be undertaken: (i) studies linking physical activity (exposure) to prioritized intermediates, and (ii) studies linking the intermediate phenotypes to reduced breast cancer risk (outcome). For the exposure–intermediate pathway search, exposures will include any type, duration, and frequency of physical activity. The prioritized biological markers related to sex steroid hormones (**Table 1**), insulin signaling (**Table 2**), and inflammation (**Table 3**), were identified in stage 1. For the intermediate–outcome search, outcomes will include any incident, invasive breast cancer. Standard controlled vocabulary (MeSH), text words and keywords will be used in the searches. The developed search strategy will be used for all databases; syntax modifications will be made to conform to individual database requirements. Reference lists of reviews will be hand searched for articles which may not have been retrieved in the search process.

Data management

References will be downloaded to Endnote X9 (Clarivate) for curation and duplicates will be removed. Covidence software (Covidence) will facilitate the review/assessment of articles by independent researchers. Stata 16 (StataCorp) will be used for meta-analysis and meta-regression where appropriate.

Selection of studies

Titles and abstracts of articles yielded by the searches will be screened for eligibility by two independent reviewers against the inclusion/exclusion criteria. Where consensus is not reached on eligibility, a third reviewer will be available for adjudication. The full text of articles deemed appropriate for inclusion will be reviewed by two independent reviewers for eligibility.

Data Extraction

Data extraction will be performed independently by two reviewers using a prepiloted system. Extracted data will include information on:

- Study design (e.g., authors, year, setting)
- Population (e.g., demographic information, health status)

- Exposure (e.g., self-reported or accelerometer-assessed physical activity) or intervention (e.g., exercise duration, frequency, intensity, time, type)
- Outcome (e.g., definition, assessment method)
- Statistical measures (e.g., analysis performed, confounders, effect estimates, confidence intervals).

Risk of bias assessment

Three separate tools will be used to assess the risk of bias (ROB) in individual studies. The Cochrane Collaboration tool, which assesses potential bias related to design, conduct, and reporting, will be applied to human RCTs (37). For nonrandomized human studies, the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) or of Exposures (ROBINS-E) tool, which assesses bias due to confounding, participant selection, measurement of exposures and outcomes, and reporting, will be used (38). A minimal set of confounding factors needed to be adjusted for in studies in order to avoid a "serious" rating for confounding when using the ROBINS-I or ROBINS-E tools (Supplementary Methods and Materials S1).

Data synthesis and analysis

Intervention and observational studies will be analyzed separately. Random effects meta-analysis of continuous outcomes (physical activity–intermediate pathways) and binary outcomes (intermediate–breast cancer pathways) will be performed for studies when the exposure, intermediate and outcome are consistently defined in ≥3 studies. Statistical heterogeneity among effect estimates will be quantified using the I^2 statistic. Meta-regression and subgroup analyses will be used, where possible, to assess whether there is heterogeneity within overall results due to differences in the study populations (e.g., exercise type, lean vs. obese participants, menopausal status, menstrual cycle stage, and breast cancer subtype). In addition, to graphically represent the dose–response effect of intermediates on breast cancer, a one-stage random-effects dose–response meta-analysis will be performed using restricted cubic splines. This method has been recently outlined and utilizes quantities and effect estimates for each category of biomarker concentrations presented in individual studies (39). Publication bias will be assessed by visual inspection of funnel plots. When meta-analysis is not possible, we may use the albatross plot (40) or a narrative synthesis will be undertaken.

Quality assessment

To rate the quality of evidence, and the strength of any findings generated, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system will be employed (41). This system rates the quality of evidence for a particular exposure–variable relationship, providing a score between very low to high based on the type of studies available, as well as their ROB, the consistency and precision of findings, directness, publication bias, effect estimates, dose–response relationships, and influence of confounding factors (41).

Discussion

The overarching aims of these systematic reviews of mechanisms are to clarify which intermediate phenotypes mediate the association between physical activity and breast cancer risk, and to appraise the strength of evidence for these pathways. The comprehensive nature of these reviews will provide robust evidence of biological plausibility, and thus strengthen causal inference.

To date, insight into potential pathways linking physical activity and breast cancer has come predominantly from narrative reviews, a small number of single-stage systematic reviews, and from individual studies (3, 9, 12, 42). Narrative reviews may be biased, and can lead to erroneous conclusions being drawn. Single stage reviews synthesize only one part of the pathway from exposure to outcome, focusing on either physical activity and intermediates (and inferring that these are robust markers of breast cancer risk) or on intermediates and breast cancer risk (with limited evidence relating to the exposures that are hypothesized to affect intermediate levels). The current two-stage reviews are distinct as they appraise the strength of evidence for both physical activity to intermediate and intermediate to breast cancer pathways. The strengths of the current approach include the use of the WCRF International and Bristol University framework for identifying and prioritizing biological intermediates, as well as the systematic synthesis (incorporating meta-analysis where possible) and appraisal of available evidence. The dose–response meta-analyses we propose represent a novel contribution to the literature. The framework has been independently validated and facilitates a two-stage review process to examine intermediates (34). Systematic review offers a rigorous scientific method for identifying and synthesizing evidence, while the GRADE system provides a structured process for appraisal the quality and strength of a body of evidence (41).

Physical activity is unlikely to affect cancer risk via a singular pathway in isolation, and it is acknowledged that the molecular pathways we focus on are interrelated (43). However, it is not within the scope of our protocol to investigate synergistic effects across multiple pathways, despite the potential for these to produce clinically meaningful risk reductions. The complex interplay between different pathways does not lend itself to systematic review.

The knowledge generated by these reviews will help to strengthen causal inference from epidemiologic data linking physical activity with a reduced risk of breast cancer. Elucidation of the mechanistic pathways may inform the optimal design of physical activity interventions to best target key intermediates in at-risk populations. Greater insight into breast cancer etiology may also facilitate the development of targeted treatment modalities and give rise to novel drug candidates. Systematic review and appraisal of these intermediate pathways will identify priority areas for future breast cancer research, and potentially divert resources away from pathways that are not supported by evidence.

Authors' Disclosures

B.M. Lynch reports grants from Wereld Kanker Onderzoek Fonds and Victorian Cancer Agency during the conduct of the study. R.L. Milne reports grants from World Cancer Research Fund during the conduct of the study. D.R. English reports grants from World Cancer Research Fund during the conduct of the study. K.A. Brown reports grants from NIH/NCI and World Cancer Research Fund during the conduct of the study. C.T.V. Swain reports grants from World Cancer Research Fund during the conduct of the study. E.H. van Roekel reports grants from Wereld Kanker Onderzoek Fonds (WKOF), as part of the World Cancer Research Fund International grant programme (grant no. 2016/1620) during the conduct of the study. T.R. Gaunt reports grants from WCRF during the conduct of the study. R.M. Martin reports grants from Cancer Research UK during the conduct of the study. No disclosures were reported by the other authors.

Acknowledgments

Funding (IIG_2018_1732) was obtained from Wereld Kanker Onderzoek Fonds (WKOF), as part of the World Cancer Research Fund International grant

programme. B.M. Lynch was supported by the Victorian Cancer Agency (MCRF18005). K.A. Brown is supported by NIH/NCI R01 CA215797. R.M. Martin was supported by the NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol. R.M. Martin was supported by a Cancer Research UK (C18281/A29019) programme grant (the Integrative Cancer Epidemiology Programme).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 5, 2021; revised August 4, 2021; accepted October 5, 2021; published first October 20, 2021.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. World Cancer Research Fund, Research American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Breast Cancer. London, UK: World Cancer Research Fund; 2017.
3. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer 2008;8:205–11.
4. Hilton HN, Clarke CL, Graham JD. Estrogen and progesterone signalling in the normal breast and its implications for cancer development. Mol Cell Endocrinol 2018;466:2–14.
5. Asi N, Mohammed K, Haydour Q, Gionfriddo MR, Vargas OLM, Prokop LJ, et al. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. Syst Rev 2016;5:121.
6. Li CI, Beaber EF, Tang MT, Porter PL, Daling JR, Malone KE. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. Cancer Res 2012;72:2028–35.
7. Takagi K, Miki Y, Ishida T, Sasano H, Suzuki T. The interplay of endocrine therapy, steroid pathways and therapeutic resistance: Importance of androgen in breast carcinoma. Mol Cell Endocrinol 2018;466:31–37.
8. Nicolás Díaz-Chico B, Germán Rodríguez F, González A, Ramírez R, Bilbao C, Cabrera de León A, et al. Androgens and androgen receptors in breast cancer. J Steroid Biochem Mol Biol 2007;105:1–15.
9. Hakimi O, Cameron LC. Effect of exercise on ovulation: a systematic review. Sports Med 2017;47:1555–67.
10. Warren MP, Perlroth NE. The effects of intense exercise on the female reproductive system. J Endocrinol 2001;170:3–11.
11. Loucks AB. Effects of exercise training on the menstrual cycle: existence and mechanisms. Med Sci Sports Exerc 1990;22:275–80.
12. Ennour-Idrissi K, Maunsell E, Diorio C. Effect of physical activity on sex hormones in women: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res 2015;17:139.
13. Lynch BM. Sedentary behavior and cancer: a systematic review of the literature and proposed biological mechanisms. Cancer Epidemiol Biomarkers Prev 2010; 19:2691–709.
14. Kang C, LeRoith D, Gallagher EJ. Diabetes, obesity, and breast cancer. Endocrinology 2018;159:3801–12.
15. Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev 2015;95:727–48.
16. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer 2015;15:484–98.
17. Stephens BR, Granados K, Zderic TW, Hamilton MT, Braun B. Effects of 1 day of inactivity on insulin action in healthy men and women: interaction with energy intake. Metabolism 2011;60:941–9.
18. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer 2010;46:2593–604.
19. Steenberg DE, Jørgensen NB, Birk JB, Sjøberg KA, Kiens B, Richter EA, et al. Exercise training reduces the insulin-sensitizing effect of a single bout of exercise in human skeletal muscle. J Physiol 2019;597:89–103.
20. Mikines KJ, Sonne B, Farrell PA, Tronier B, Galbo H. Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am J Physiol 1988;254: E248–259.
21. Frosig C, Rose AJ, Treebak JT, Kiens B, Richter EA, Wojtaszewski JF. Effects of endurance exercise training on insulin signaling in human skeletal muscle: interactions at the level of phosphatidylinositol 3-kinase, Akt, and AS160. Diabetes 2007;56:2093–102.
22. Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JF, Dela F. Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. Diabetes 2004;53: 294–305.
23. Neilson HK, Conroy SM, Friedenreich CM. The influence of energetic factors on biomarkers of postmenopausal breast cancer risk. Curr Nutr Rep 2014;3: 22–34.
24. Neilson HK, Friedenreich CM, Brockton NT, Millikan RC. Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research. Cancer Epidemiol Biomarkers Prev 2009;18:11–27.
25. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.
26. Antuna-Puente B, Feve B, Fellahi S, Bastard JP. Adipokines: the missing link between insulin resistance and obesity. Diabetes Metab 2008;34:2–11.
27. Hamilton MT, Healy GN, Dunstan DW, Zderic TW, Owen N. Too little exercise and too much sitting: inactivity physiology and the need for new recommendations on sedentary behavior. Curr Cardiovasc Risk Rep 2008;2:292–8.
28. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation 2007;116:1234–41.
29. Parsons TJ, Sartini C, Welsh P, Sattar N, Ash S, Lennon LT, et al. Physical activity, sedentary behavior, and inflammatory and hemostatic markers in men. Med Sci Sports Exerc 2017;49:459–65.
30. Autenrieth C, Schneider A, Döring A, Meisinger C, Herder C, Koenig W, et al. Association between different domains of physical activity and markers of inflammation. Med Sci Sports Exerc 2009;41:1706–13.
31. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol 2005;98:1154–62.
32. You T, Arsenis NC, Disanzo BL, Lamonte MJ. Effects of exercise training on chronic inflammation in obesity: current evidence and potential mechanisms. Sports Med 2013;43:243–56.
33. Lewis SJ, Gardner M, Higgins J, Holly JMP, Gaunt TR, Perks CM, et al. Developing the WCRF International/University of Bristol methodology for identifying and carrying out systematic reviews of mechanisms of exposure-cancer associations. Cancer Epidemiol Biomarkers Prev 2017;26:1667–75.
34. Ertaylan G, Le Cornet C, van Roekel EH, Jung AY, Bours MJL, Damms-Machado A, et al. A comparative study on the WCRF International/ University of Bristol methodology for systematic reviews of mechanisms underpinning exposure-cancer associations. Cancer Epidemiol Biomarkers Prev 2017;26:1583–94.
35. University of Bristol. TeMMPo - Text Mining for Mechanism Prioritisation. Available from: https://www.temmpo.org.uk/.
36. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6:e1000097.
37. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
38. University of Bristol. The ROBINS-E tool. Available from: https://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/.
39. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. Stat Methods Med Res 2019;28: 1579–96.
40. Harrison S, Jones HE, Martin RM, Lewis SJ, Higgins JPT. The albatross plot: a novel graphical tool for presenting results of diversely reported studies in a systematic review. Res Synth Methods 2017;8:281–9.
41. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
42. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer 2017;17:620.
43. Lynch BM, Leitzmann M. An evaluation of the evidence relating to physical inactivity, sedentary behavior, and cancer incidence and mortality. Curr Epidemiol Rep 2017;4:221–31.